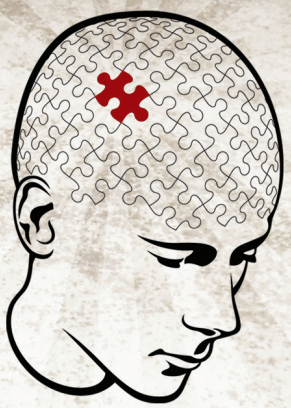

SUBSTANCE USE AND ABUSE IN SOUTH AFRICA

Insights from Brain and Behavioural Sciences

Editors: George F.R. Ellis, Dan J. Stein, Kevin G.F. Thomas, Ernesta M. Meintjes

Substance Use and Abuse in South Africa

Insights from Brain and Behavioural Sciences

Editors
George F.R. Ellis, Dan J. Stein,
Kevin G.F. Thomas, Ernesta M. Meintjes

Substance Use and Abuse in South Africa: Insights from Brain and Behavioural Sciences
First Published 2013
Print published in 2012 in South Africa by UCT Press

First Floor, Sunclare Building,
21 Dreyer Street, Claremont,
7708
South Africa
© 2013 UCT Press

ISBN 978 1 91989 529 1 (Parent)
ISBN 978 1 92054 164 4 (WebPDF)

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage or retrieval system, without prior permission in writing from the publisher. Subject to any applicable licensing terms and conditions in the case of electronically supplied publications, a person may engage in fair dealing with a copy of this publication for his or her personal or private use, or his or her research or private study. See Section 12(1)(a) of the Copyright Act 98 of 1978.

Project manager and editor: Alfred LeMaitre
Proofreader: Glenda Younge
Typesetter: Exemplarr Worldwide Ltd, Chennai
Cover designer: Marius Roux
Indexer: Ethné Clarke

The authors and the publisher have made every effort to obtain permission for and to acknowledge the use of copyright material. Should any infringement of copyright have occurred, please contact the publisher and every effort will be made to rectify omissions or errors in the event of a reprint or new edition
.
This book has been independently peer-reviewed by academics who are experts in the field.

Contents

Preface

The arrival of democracy in South Africa was a wonderful victory for the country, and for the world. Nevertheless, the decades of apartheid left many wounds that require ongoing attention. One of the most under-recognised of these, perhaps, is the high prevalence of alcohol and substance use disorders in some of our communities. Recent epidemiological data have highlighted the extent to which conditions such as fetal alcohol syndrome are present, and the tremendous suffering and impairment that they cause.

Substance use disorders are, of course, a universal scourge. We have much to understand about the individual differences which create vulnerabilities to these conditions. At the same time, these disorders have somewhat different risk factors, and they are experienced and expressed somewhat differently in different socio-cultural contexts. The use and abuse of alcohol in South Africa is intimately bound up with the political history of the country, and alcohol continues to be used and abused in somewhat different ways in different communities in South Africa.

Increasingly we are understanding that substance use disorders are a major public health problem; there is also value to considering these conditions as brain disorders, which require appropriate professional help. Effective and cost-effective prevention is of course a crucial goal to strive for. At the same time, once addiction is present, then evidence-based treatments are required. The current treatment gap in South Africa is unacceptable; there are too few services for too many. There is a great need to improve health and mental health literacy in the community, and to train addiction professionals.

For these reasons, I am delighted to see this volume. It covers a wide range of aspects of substance use and abuse in South Africa, ranging from the neurobiology and neuropsychology of substance use disorders, through to clinical diagnosis and treatment, and on to epidemiology and public health policy. The editors are leaders of the University of Cape Town's Brain-Behaviour Initiative, and their integrative approach to the brain-mind and its disorders has helped drive the volume. I hope it will succeed in its aim of informing the South African public, as well as addiction professionals in training.

Mamphela Ramphele

About the contributors

Colleen M. Adnams is the Vera Grover Professor of Intellectual Disability in the Department of Psychiatry and Mental Health, University of Cape Town, and Chief Specialist, Intellectual Disability Services, Provincial Government Western Cape Associated Psychiatric Hospitals. With a background in neurodevelomental paediatrics, she has contributed to numerous provincial, national and international committees and task groups related to service provision, training, policy and the study of developmental and intellectual disabilities. She has a research interest in fetal alcohol spectrum disorder and is active in international collaborations focusing on epidemiological and neurobehavioural aspects of this major public health problem in South Africa.

Paul Carey is Associate Professor in Psychiatry, Department of Psychiatry, University of Stellenbosch. His research interests include brain imaging of substance abuse, and general psychopharmacology.

Shareefa Dalvie is a PhD student in Human Genetics at the University of Cape Town. Her current research interests include the genetic basis of complex behavioural and psychiatric disorders, such as alcohol and methamphetamine ('tik') dependence and bipolar disorder. Shareefa completed her BSc degree, majoring in Genetics and Development and Physiology, at UCT in 2007. She completed both her Honours and Master's degrees in the Division of Human Genetics. Both of these projects investigated the association of selected candidate genes with the diagnosis of bipolar disorder Type I.

William M.U. Daniels graduated in 1983 with a BSc degree in Biochemistry and Botany from the University of the Western Cape. He later obtained his BSc (Hons) (1985) and MSc (1988) in Medical Biochemistry, a PhD in Chemical Pathology (1993) and an MBA (2003) in Business Administration at the University of Stellenbosch. He completed his postdoctoral studies at the University of Texas Health Science Center in San Antonio. He has held numerous appointments, including senior scientist in the Department of Chemical Pathology at Tygerberg Hospital (1986–1996) and head of the Department of Medical Physiology, University of Stellenbosch (1996–2007). Currently, Professor Daniels heads the School of Medical Sciences at the University of KwaZulu-Natal. His research interests include neuroproteomics, behavioural neuroscience, neurodegenerative diseases and stress and anxiety disorders.

Jacqueline J. Dimatelis completed her undergraduate studies (BSc in Physiology and Psychology) in 2000 at the University of Stellenbosch, followed by an Honours degree in Psychology in 2001, after which she worked in the United Kingdom at facilities catering for the mentally ill. On returning, she completed an MSc in Neuroscience at the University of Stellenbosch in 2006. Her MSc studies focused on the effects of early life stress and additional stress exposures later in life on behaviour and neurochemistry of the hippocampus. She completed her PhD in 2009, also at the University of Stellenbosch, on the effects of early life stress on later life drug addiction, and particularly on methamphetamine, which has become the drug of choice for abuse in South Africa. She is currently a postdoctoral fellow at the University of Cape Town under the guidance and supervision of Professor Vivienne Russell, investigating the protein role-players in animal models of depression.

George F.R. Ellis FRS, Emeritus Professor of Applied Mathematics and Honorary Research Associate in the Mathematics Department, University of Cape Town, works on general relativity theory, cosmology, complex systems and the way physics underlies the functioning of the human brain. He was co-author, with Stephen Hawking, of *The Large Scale Structure of Space-Time* and, with Nancey Murphy, of *On the Moral Nature of the Universe*. He is past president of the International Society of General Relativity and Gravitation, the Royal Society of South Africa and the International Society of Science and Religion, a founder member of the South African Academy of Science, and a Fellow of both the Third World Academy of Science and of the Royal Society, London. He is Joint Editor in Chief of the *Journal of General Relativity and Gravitation*. He has been awarded the Herschel Medal of the Royal Society of South Africa, the Star of South Africa Medal (awarded by President Nelson Mandela), the Templeton Prize (2004), the South African National Science and Technology Forum lifetime contribution award, the SA Institute of Physics de Beers Gold medal, the Academy of Science of South Africa Gold Medal and the Order of Mapungubwe (awarded by President Thabo Mbeki).

Helen Ferrett is a clinical psychologist employed at the Psychiatry Department of the University of Stellenbosch and the Medical Research Council's Unit of Stress and Anxiety Disorders. Her research is primarily in the field of cognitive assessment. Her specific research interests are cross-cultural cognitive assessment, the development of culturally- and linguistically-fair tests and normative data, and the neurocognitive profiling of adolescents with alcohol and other substance use disorders.

Alan J. Flisher was a child and adolescent psychiatrist. He was the Sue Streungmann Professor of Child and Adolescent Psychiatry and Mental Health at the University of Cape Town; head of the Division of Child and Adolescent Psychiatry at UCT and Red Cross War Memorial Children's Hospital; Director of the Adolescent Health Research Unit at UCT; Honorary Senior Research Fellow at the Health Systems Research Unit at the Medical Research Council; Adjunct Professor at the Research Centre for Health Promotion at the University of Bergen, Norway; and Director of the Mental Health and Poverty Research Programme Consortium. From 1994 to 1996, he was a research scientist at the New York State Psychiatric Institute. He held visiting appointments at Columbia University, the

University of Oslo and Leeds University, and was a Takemi Fellow at Harvard University. His research interests included adolescent health, mental health services research and psychiatric epidemiology. His research output included 200 papers in peer-reviewed journals, 50 books or chapters and 400 conference presentations. He was editor of the *Journal of Child and Adolescent Mental Health*, and conducted extensive policy development consultancies nationally and internationally.

Noxolo Hewana is a research officer in the Department of Psychiatry and Mental Health at the University of Cape Town. In this capacity, she has conducted literature searches for the development of national policy guidelines for adolescent and youth health, for the National Department of Health. Prior to this appointment she worked in the Social Aspects of HIV/AIDS and Health research programme at the Human Sciences Research Council (HSRC).

Anthony Hodge has an MA in Psychological Research from the University of Cape Town. His research interests and areas of expertise include sleep, creativity, health psychology and clinical neuropsychology.

Fleur Howells is a postdoctoral research fellow in the Department of Psychiatry at the University of Cape Town. She graduated with a doctoral degree in 2009, in the Department of Human Biology. Her PhD and subsequent work have led to several articles in international neuroscience journals. Her research interests focus on understanding the neural circuitry underlying psychiatric disorders, using both multimodal imaging approaches in clinical populations and various methodologies in animal models.

Jonathan Ipser received an MA in Psychological Research from the Department of Psychology at UCT in 2002. He recently submitted his PhD thesis to UCT's Department of Psychiatry on the topic of the relationship between impulsivity, affect and early psychological adversity. Jonathan is actively involved in a number of neuroscience research programmes, many of which were initiated during his term as Project Manager for the Brain-Behaviour Initiative. He was awarded a postdoctoral fellowship in 2010 by the National Institute on Drug Abuse/International AIDS Society to conduct research into HIV-associated neurocognitive disorders at the HIV Neurobehavioral Research Center (HNRC) of the University of California at San Diego.

David Kibel is currently a psychiatrist in private practice in Cape Town. He trained in medicine at the University of Cape Town, and in psychiatry in the United Kingdom, before taking a post as lecturer in the Department of Psychiatry at the University of Cape Town. He has had an interest in evolutionary psychiatry for a long time and this interest continues to inform his work.

Crick Lund is an associate professor in the Department of Psychiatry and Mental Health at the University of Cape Town, and is Director of the Centre for Public Mental Health. He was involved in developing the first post-apartheid norms for mental health services in South Africa, and subsequently worked for five years for the World Health Organization, where he contributed to developing the WHO Mental Health Policy and Service Guidance package, and consulted to several low- and middle-income countries (LMICs) in the development of mental health policies and plans. Since 2005, he has coordinated the Mental Health and

Poverty Project, a study investigating mental health policy development and implementation in four African countries. His research interests include mental health policy, services and poverty.

Susan Malcolm-Smith is a lecturer in the Department of Psychology at the University of Cape Town, and a member of ACSENT (Applied Cognitive Science and Experimental Neuropsychology Team). She trained in neuropsychology, and teaches this and quantitative research methods at undergraduate and postgraduate levels. Her research focuses on basic emotion in the brain, and how this regulates social functioning. She is currently completing a PhD, which examines the impact of early social trauma on long-term opioid system and mood dysregulation.

Ernesta M. Meintjes is the South African Research Chair in Brain Imaging at the University of Cape Town and an associate professor of Biomedical Engineering, MRC/UCT Medical Imaging Research Unit, in UCT's Department of Human Biology. She holds a PhD in Physics from Oregon State University. She joined the Biomedical Engineering Department at the University of Cape Town in 1998, where she established a new research focus in magnetic resonance imaging (MRI). Her research interests include neuroimaging studies of children with fetal alcohol spectrum disorder and HIV, sequence development to optimise paediatric scanning through real-time motion and shim correction, and cardiovascular MRI.

Neo Morojele has a PhD in Psychology from the University of Kent at Canterbury. She attended a postdoctoral programme on adolescent substance abuse research at Mount Sinai School of Medicine in New York from 1998 to 1999. Her current research focuses on the links between alcohol use, sexual risk behaviour and HIV, substance abuse among adolescents and youth, and the prevention of fetal alcohol spectrum disorders (FASD) in South Africa. She has published extensively in social science, public health and addiction journals, and has authored/co-authored five book chapters. She is a member of the international advisory board of the *Journal of Substance Use* and an associate editor of the *African Journal of Drug and Alcohol Studies*.

Bronwyn Myers is a specialist scientist in the Alcohol and Drug Abuse Research Unit of the South African Medical Research Council, where she heads up the Treatment and other Interventions research sub-stream. This unit is arguably the leading research unit for addictions in Africa. Professor Myers has a PhD in clinical psychology and 10 years of addictions research experience. She has been a co-principal investigator with US colleagues on several NIH-funded pilot and large-scale, randomised controlled trials on behavioural HIV and substance use, risk-reduction interventions for vulnerable, substance-using women and their sex partners. Professor Myers also has considerable experience as an addictions clinician, and has an honorary appointment with the University of Cape Town's Department of Psychiatry and Mental Health, where she maintains teaching/supervision duties. Her expertise in substance abuse treatment and HIV has been acknowledged via invitations to serve on international reference groups on HIV and drug use, and working groups on the development and assessment of global substance abuse treatment services. She has written prolifically on the subject.

Jaak Panksepp is Baily Endowed Professor of Animal Well-Being Science at the College of Veterinary Medicine at Washington State University and Distinguished Research Professor of Psychobiology, Emeritus, at Bowling Green State University, as well as Head of Affective Neuroscience Research at the Falk Center for Molecular Therapeutics at Northwestern University. He is best known for his pioneering book, *Affective Neuroscience*.

Eleni Pantelis is a research assistant at the University of Cape Town and Convener of Clinical Neuropsychology Services at Groote Schuur Hospital. She is currently researching human homologues of the basic emotion command systems identified in other mammals.

Karl Peltzer is Research Director in the research programme HIV/AIDS/STI and TB (HAST), Human Sciences Research Council, South Africa. He is a prevention researcher and evaluator with over 20 years of experience in the study of health promotion, risk behaviour and disease prevention, and socio-behavioural interventions. Dr Peltzer has published extensively on health behaviour and health interventions (13 books and 300 articles). He has worked extensively on public health issues of substance use, cancer, tuberculosis and HIV control, as well as nutrition, physical activity, hypertension, mental health, injury and violence prevention and health promotion.

Willem Pienaar attended the University of Stellenbosch, qualifying as a medical doctor in 1974. He spent five years as a general practitioner in Victoria West, and then returned to the University of Stellenbosch, where he qualified as a psychiatrist in 1984 and completed an MD in Psychiatry in 1992. He earned an MPhil in Bioethics from the Department of Philosophy at Stellenbosch, and by peer review is a Fellow of the South African College of Psychiatry. His special interests are substance abuse treatment, bioethics and philosophy.

Cleo Protogerou is a health psychologist currently based at the University of Cape Town. Her research interests include health risk-taking attitudes and behaviours in young people and, in particular, the psychological, social and cultural factors that influence university students' safe-sex decisions and behaviours. Her research, conducted in academic and applied settings in Greece, Britain and South Africa, has been presented in international conferences, and is currently being published. She has also worked for the Greek Organisation Against Drugs (OKANA), designing and implementing drug prevention programmes in primary and secondary education.

Shandir Ramlagan is Chief Researcher in the HIV/AIDS/STIs and TB research programme. He obtained his Master's in Development Studies from the University of Natal. He has experience in social science research, especially in the areas of qualitative research design and methodology, planning and management of surveys, and design of research instruments. His project experience includes work for organisations such as the W.K. Kellogg Foundation, Nelson Mandela Children's Fund, the World Bank, Population Council and various government departments. Shandir's publication record spans progress reports, co-authored chapters for SIDA and the World Bank, literature reviews, and co-authored peer-reviewed journal articles, and conceptual and epidemiological models.

Eileen Rich has a Master's degree in Research Psychology, which she obtained from the University of South Africa (UNISA). Currently, she is employed as a senior scientist with the Medical Research Council's Alcohol & Drug Abuse Research Unit (Pretoria) and is involved with a pilot HIV Prevention Intervention study based in bars and shebeens in rural areas of North West province.

Don Ross is Professor of Economics and Dean of Commerce at the University of Cape Town. He is also Research Fellow at the Center for Economic Analysis of Risk at Georgia State University. His current areas of research concentration are the experimental economics and neuroeconomics of impulsive choice, game-theoretic foundations of sociality, trade and industry policy in Africa, and the relationship between metaphysics and science. He is the author of numerous articles and 13 books, including, most recently, *What is Addiction?* (co-edited with H. Kincaid, D. Spurrett and P. Collins); *Midbrain Mutiny: The Picoeconomics and Neuroeconomics of Disordered Gambling* (with C. Sharp, R. Vuchinich and D. Spurrett); *Every Thing Must Go: Metaphysics Naturalized* (with J. Ladyman); and *The Oxford Handbook of Philosophy of Economics* (co-edited with H. Kincaid).

Vivienne Ann Russell graduated with BSc, BSc(HONS) and MSc degrees in Chemistry at the University of Cape Town. She joined the research group of Professor Brian Shanley at Tygerberg Hospital, University of Stellenbosch, where she completed her PhD in 1978 on the neurochemistry of acute porphyria, a genetic disorder which causes acute episodes of neural dysfunction. She demonstrated the neurotoxicity of the porphyrin precursors that accumulate during an acute attack. She subsequently joined the University of Cape Town, was promoted to Professor in 2004 and Fellow of the University of Cape Town in 2008. She is the author of more than 100 scientific papers and several chapters in books, and has been invited speaker at several national and international scientific meetings. Her research has focused on animal models of mental disorders, including attention-deficit/hyperactivity disorder (ADHD), depression, stress and exercise. She has played a major role in promoting neuroscience training in Africa.

Mark Solms is Professor in Neuropsychology at the University of Cape Town and Co-Chair (with Jaak Panksepp) of the International Neuropsychoanalysis Society. He is best known for his elucidation of the forebrain mechanisms of dreaming and for his efforts to integrate psychoanalytic theories and methods with those of modern neuroscience.

Katherine Sorsdahl is a postdoctoral Fellow in the Department of Psychiatry and Mental Health at the University of Cape Town. Her main research interests involve improving access to mental health services and increasing the quality of services in South Africa, with a recent focus on substance use.

Dan J. Stein is Professor and Head of the Department of Psychiatry and Mental Health at the University of Cape Town. His main research interest lies in anxiety disorders, and he is Director of the Medical Research (MRC) Unit on Anxiety and Stress Disorders. In his role as Director of the University of Cape Town's Brain-Behaviour Initiative, he has increasingly mentored work in basic and clinical neuroscience research that is particularly relevant to South Africa, including substance use disorders and neuroHIV/AIDS.

Henk Temmingh is a consultant psychiatrist at Valkenberg Psychiatric Hospital and a lecturer in the Department of Psychiatry and Mental Health at the University of Cape Town. He specialises in the treatment of patients with schizophrenia, bipolar disorder and related psychotic disorders, and has a special interest in the treatment of patients with severe mental illness and co-occurring substance use disorders. He is also a consultant psychiatrist to the Cape Town Drug Counselling Centre.

Kevin G.F. Thomas is a senior lecturer in the Department of Psychology at the University of Cape Town. He completed a postdoctoral clinical internship in Neuropsychology at the University of Florida in 2002. His main research interests are in the fields of clinical, cognitive and experimental neuropsychology, with particular focus on the effects of trauma and stress on short- and long-term cognitive functioning, and on cognitive impairments in adolescent alcohol abusers. He is a member of the South African Clinical Neuropsychological Association and the Psychological Society of South Africa, and serves on executive committees for both these bodies.

Anne Uhlmann graduated with an MA (Diplom) in Biology at the Humboldt University of Berlin, where she specialised in brain physiology and brain imaging. Her research areas included the somatosensory system and working memory. She is currently doing her PhD in the Department of Psychiatry at the University of Cape Town, and works as a research assistant for the Brain-Behaviour Initiative at UCT. The topic of her research is the neural correlates of deficits in affect regulation in methamphetamine abusers with and without a history of psychosis.

Bavanisha Vythilingum was a senior psychiatrist in the Department of Psychiatry at UCT, and Director of the Division of Consultation Liaison Psychiatry and Women's Mental Health until June 2011. She is now a part-time senior psychiatrist in the division.

Catherine Ward is a senior lecturer in the Department of Psychology, University of Cape Town. Her interests lie in violence prevention (including reducing the – violent – harms caused by substance misuse).

Allanah Wilson trained in Medicine at the University of Cape Town, and has an interest in addiction medicine. She is currently doing her community service.

Don Wilson is a general psychiatrist with an interest in addictions. He is the co-director of the Addictions division in the Department of Psychiatry, Unversity of Cape Town.

Introduction: substance use and abuse in South Africa

Dan J. Stein, George F.R. Ellis, Ernesta M. Meintjes and Kevin G.F. Thomas

Since humans evolved in Africa, it is probable that the first human experience of psychotropic substances also occurred on this continent. Certainly, psychotropic substances have been used by humans for thousands of years – for recreational, spiritual and other potentially positive reasons. Simultaneously, the negative consequences of such substance use have long been noted, with early texts from the Bible to Hippocrates providing detailed accounts of their effects. Today, in much of the world, and arguably in South Africa in particular, the adverse consequences of substance use are particularly apparent.

According to the World Mental Health Survey, which included the first nationally representative epidemiological data on common mental disorders in Africa, South Africa has one of the highest lifetime prevalences of substance use disorders across the globe (Kessler et al, 2007). The most commonly used substance in South Africa, unsurprisingly given our history, is alcohol (Van Heerden et al, 2009), and the incidence of fetal alcohol syndrome in the country is perhaps the highest in the world (May et al, 2007). There is also evidence of the increasing use of a range of other substances, including methamphetamine ('tik') and heroin (Parry et al, 2004).

The rise on substance use disorders is associated with increased severity of a range of negative outcomes, both globally and locally. These include other medical and psychiatric disorders, risky sexual behaviour and sexually transmitted diseases, crime and violence, family dysfunction, and various 'accidents', including motor vehicle collisions. Given the high rate of past political and current domestic violence in South Africa (Gupta et al, 2008; Kaminer et al, 2001), the association between substances and aggression is of particular concern. The association between substances and risky sexual behaviour is at least as worrying (Simbayi et al, 2009) in southern Africa, which has the world's highest rates of HIV/AIDS.

Also of significant concern is the lack of access to effective treatments for substance use disorders in many parts of the globe, including South Africa. There are a range of barriers to treatment, including structural and attitudinal barriers. Structural barriers include the relative lack of funding for mental health clinicians and the relative lack of accessible facilities for the treatment of substance use disorders. Underlying these barriers, however, are likely to be attitudinal barriers on the part of policy-makers, patients and even clinicians. Although there is growing evidence to support the concept that substance use disorders are medical disorders (World Health Organization, 2001), these conditions are highly stigmatised, and are often viewed as falling with the purview of Departments of Social Welfare, rather than Departments of Health.

The prevalence of substance use disorders in South Africa, their associated morbidity, and their underdiagnosis and undertreatment, makes a volume that focuses on these conditions essential. But there are several more reasons for such a book, and these include the enormous range of advances in our understanding of substance use disorders and their treatment, as well as the need for different disciplines to come together to understand these conditions and to make the largest possible impact on reducing them. In particular, advances in molecular and cognitive-affective neuroscience have the potential to enable us to understand these issues more thoroughly, and so tackle them in innovative ways. Indeed, this volume emerged from research within the Brain-Behaviour Initiative at the University of Cape Town. We aim here to make that link explicit.

In the remainder of this introductory chapter, we will introduce the different authors of this volume, and their different disciplines and perspectives, focusing not only on the epidemiology and symptomatology of substances, but also on some of these advances and multi-disciplinary opportunities. This will serve to introduce not only the chapters of the volume, but also provide a brief rationale for the editors' emphasis on the need for an integrative approach to substance use and its disorders.

Epidemiology and symptomatology

Recent epidemiological work has been crucially important in providing rigorous data to show the prevalence of substance use disorders and their morbidity in South Africa. Karl Pelzer has been a prolific researcher in South Africa, carrying out a broad range of surveys in the area of clinical psychology. In Chapter 1, he and Shandir Ramlagan summarise data on the epidemiology of substance use disorders in South Africa, focusing in particular on the work that they have undertaken.

Clinicians see only the tip of the iceberg documented by community studies. Nevertheless, this tip is of crucial importance, given its associated severity of symptoms. In Chapter 2, Don Wilson and Henk Temmingh, clinicians who work in the area of addiction psychiatry, describe the clinical presentation of substance abuse and dependence in the South African context. Colleen Adnams, Professor of Intellectual Disability, describes in Chapter 3 the developmental consequences of exposure to substances, focusing in particular on fetal alcohol syndrome.

South Africa's youth are a particularly important population to consider when thinking about substance use. The vast majority of substance use disorders begin in adolescence and early adulthood. Neo Morejele, Eileen Rich, Alan Flisher and Bronwyn Myers have particular interest and expertise in this population, and in Chapter 13 they review the relevant epidemiology, including prevalence, morbidity and risk and protective factors, with a focus on the relevant South African studies. We now know that adolescents respond to rewards in a different way from adults, and their developing brains may be particularly sensitive to damage after substances (see Figure 1). The authors emphasise the relative dearth of appropriate treatment programmes for young people in South Africa, and provide a research agenda for the future.

One dogma of psychiatric epidemiology is that substance use disorders are more common in men, while mood and anxiety disorders are more common in women. It is noteworthy that

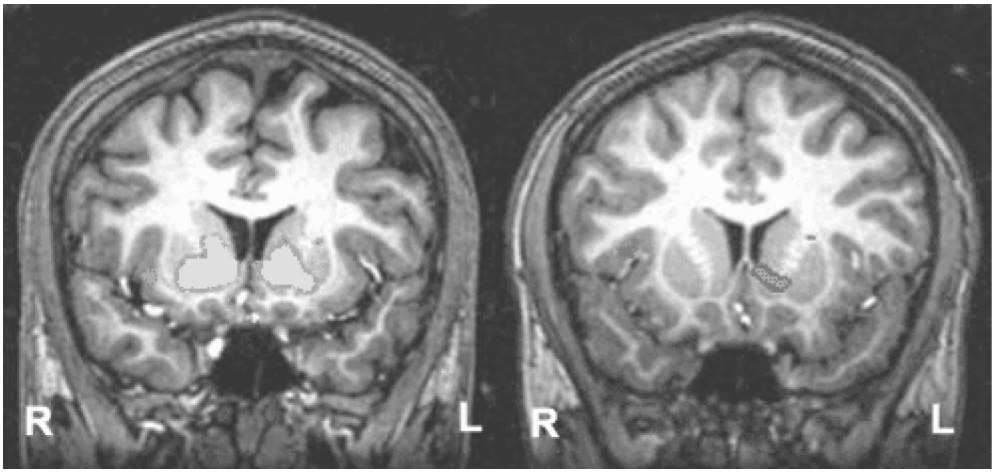

Figure 1: Functional magnetic resonance imaging, showing differences in young adults (left) and in adolescents (right) during reward anticipation
Source: http://www.niaaa.nih.gov/Resources/GraphicsGallery/Neuroscience/adolescent.htm

this dogma is currently being overturned. It seems that as women become more empowered in social structures, so there is a shift in psychiatric epidemiology, with substance use by women becoming more common. Several other gender issues play a key role in the thinking about substance use disorders and services, including the greater vulnerability of women to substance-related gender violence, and to the adverse consequence of problem drinking. In Chapter 4, Bronwyn Myers, an addiction specialist, and Bavanisha Vythilingum, a consultation-liaison psychiatrist with a particular interest in women's mental health, provide a comprehensive overview.

Neuroscience and psychology

Psychobiological explanations include those which focus on distal mechanisms (that is, the mechanisms uncovered by evolutionary theory) and proximal mechanisms (that is, the mechanisms uncovered by researchers working on the areas of neuroanatomy, neurochemistry, neurogenetics and neuropsychology). In the case of substance use and its disorders, there has been growing interest and advances in our understanding of both distal and proximal explanations.

In Chapter 5, David Kibel and Dan J. Stein, psychiatrists with strong interests in evolution theory, begin by discussing the contribution of such theory to conceptualising substance use and its disorders. Although evolutionary medicine is a relatively new perspective in the medical sciences, it is arguably a particularly powerful one, as exemplified by their discussion. They note that reward systems have evolved over time, as a key mechanism for enhancing survival. It turns out that substances 'hijack' the reward system, accounting for their tremendously powerful effects (animals may self-administer substances to the point where they die from starvation). This kind of understanding leads to new ways of conceptualising the prevention and treatment of substance use disorders.

Evolutionary mechanisms are passed down from generation to generation by our genes, with individual variation allowing for more successful mechanisms to evolve. There is a growing understanding of the way in which genes mediate our reward system in general, and substance use disorders in particular. In Chapter 6, Shareefa Dalvie and Fleur Howells, postgraduate students working with Rajkumar Ramesar, a Professor of Human Genetics, provide a comprehensive overview of this material.

Genes are ultimately responsible for protein synthesis, and brain proteins in turn underpin the structure and function of the brain's neuronal circuits. Perhaps one of the most exciting series of advances in neuroscience in the past few decades has been the development of imaging technologies for neuronal structure and function. Of particular interest to this volume is work that has focused on reward systems and on the changes brought about by substance use and its disorders. For example, the dopaminergic system (see Figure 2) is implicated in reward processing, and brain imaging studies demonstrate that substances of abuse markedly affect dopamine receptors (see Figure 3).

The dopamine system is implicated in conditioning, and in Chapter 7 Ernesta M. Meintjes, a Professor of Brain Imaging, and her colleagues synthesise the relevant material,

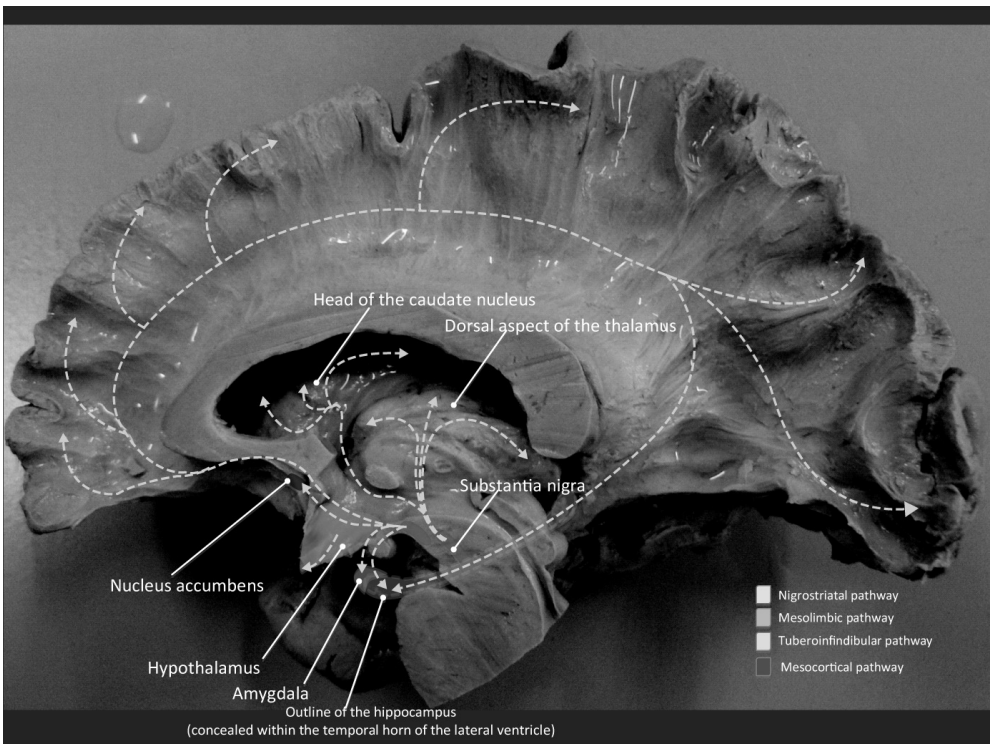

Figure 2: The circuits of the dopaminergic system. Mesolimbic and mesocortical circuits originate in subcortical areas and spread diffusely; these are thought to play a particularly important role in reward.

Source: courtesy of Coenraad Hattingh

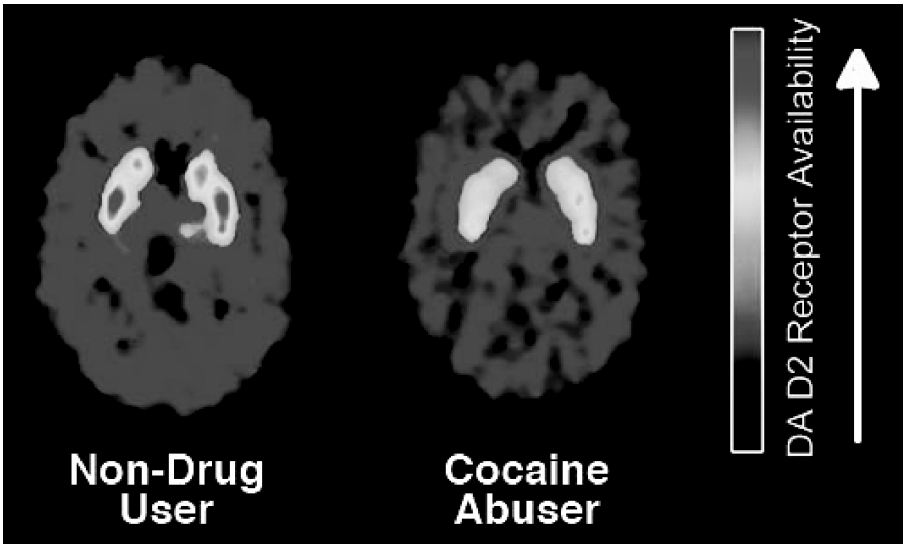

Figure 3: Decreased dopamine (D_2) receptors in the brain of a person addicted to cocaine versus a non-drug user

Source: http://www.nida.nih.gov/ResearchReports/Cocaine/effects.html#short

focusing in particular on brain imaging studies of methamphetamine, motivation and alterations that may contribute to diminished sensitivity to natural rewards in addicted patients.

An integrative cognitive-affective neuroscience perspective, which draws on a variety of sciences, ranging from the molecular through to the cognitive-affective, is arguably needed for each of the major substances. Methamphetamine, although relatively new to South Africa, has become of increasing significance. It has a specific and well-understood mechanism of action, perhaps facilitating the development of such an integrative account. Susan Malcolm-Smith, Anne Uhlmann, Anthony Hodge and Jonathan Ipser have backgrounds in experimental psychology, and in Chapter 8 they provide a useful multidisciplinary approach to conceptualising methamphetamine abuse, including the mechanisms underlying methamphetamine vulnerability and sequelae.

Specific molecules and circuits underpin the way in which our cognitions and affects operate (see Figure 3). In Chapter 9, neuropsychologists Kevin Thomas and Helen Ferrett describe the way in which substance use leads to impairments in multiple domains of psychological function. In Chapter 10, Mark Solms, a leading neuropsychoanalyst, his student Eleni Pantelis and Jaak Panksepp, a pioneer in affective neuroscience, reframe some early remarks by Freud in terms of current neuroscience, providing an innovative approach to substance use disorders. In Chapter 11, Don Ross, a Professor of Economics with a strong interest in neuroeconomics, reviews the question of how current work on choice and decision-making influences our thinking about substance use.

Although animal models of psychiatric disorders arguably always remain a step away from the human condition, given the complexity of the human brain-mind, we are closely enough related to rodents and non-human primates that animal work is able to

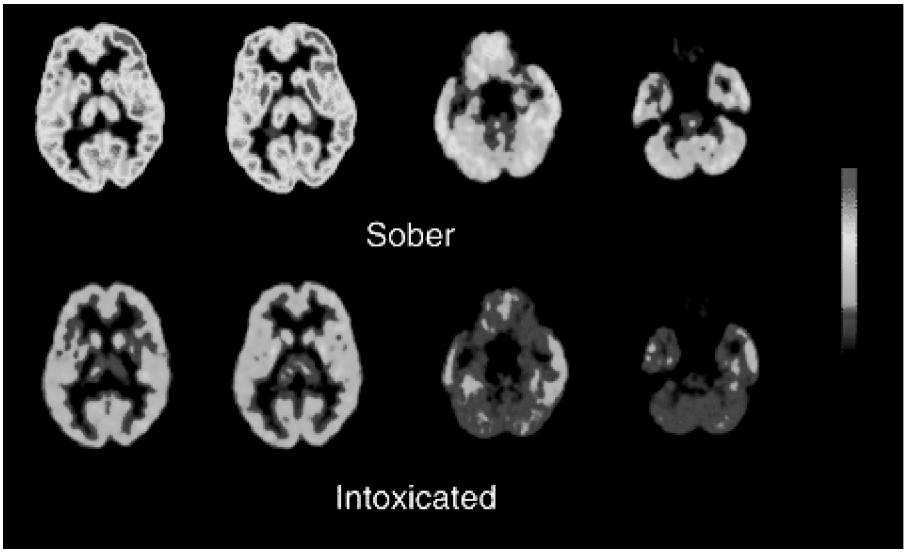

Figure 4: Alcohol drinking markedly reduces brain metabolism
Source: http://www.niaaa.nih.gov/Resources/GraphicsGallery/Neuroscience/brain_activity.htm

shed considerable light on the mechanisms involved in substance use and its disorders. Professors Vivienne Russell, a neurochemist, William Daniels, a neurophysiologist, and Jacqueline Dimataelis, a postdoctoral fellow who has worked with both, provide a detailed account of this set of research in Chapter 12, noting how animal models are able to model the major stages of drug addiction (preoccupation/anticipation, binge/intoxication and withdrawal).

Intervention and policy

What matters, as Marx wrote, is not merely to understand the world, but to change it. In the last section of this volume, we address the question of how best to prevent and treat substance use disorders. Cleo Protogerou, Alan Flisher and Neo Morejele have backgrounds in psychology and psychiatry, and in Chapter 14 provide a comprehensive review of the data on prevention of substance use in youth. Unfortunately, the need for change is more easily expressed than implemented. Indeed, these authors note that local rigorously designed studies have tended to show at best modest effects of intervention. They do, however, provide valuable practical suggestions for future studies in this area.

In Chapter 15, Catherine Ward, a psychologist interested in issues of prevention, goes on to review the sociology of substance use in South Africa, focusing in particular on interpersonal violence. Katherine Sorsdahl, who has a background in behavioural psychology, and Dan Stein, a psychiatrist, address in Chapter 16 the issue of stigmatisation of substance use, arguing that there is a need to increase clinician and public mental health literacy in this area. In Chapter 17, Willem Pienaar, a psychiatrist with a strong interest in medical ethics, reviews the ethical issues surrounding substance use and substance use disorders.

In Chapter 18, Henk Temmingh and Bronwyn Myers review the evidence on the pharmacotherapy and psychotherapy of substance use disorders. Researchers in this area are fortunate in that a significant research database of randomised controlled trials, often undertaken in academic settings, allows for the formulation of an evidence-based approach to the treatment of these conditions. At the same time, it is clear that much more work is needed, particularly in order to develop approaches that are effective in real-world settings, including low- and middle-income countries.

Finally, in Chapter 19, Crick Lund and Noxolo Hewana discuss appropriate policies and laws to address substance use in South Africa. Lund has particular expertise and experience in the area of public and community mental health. They provide a conceptual introduction to policy, and detail the challenges faced in developing and implementing substance use policies. They also provide a historical overview of substance abuse policy and legislation in South Africa, ranging from apartheid-era legislation through to the recent Prevention of and Treatment for Substance Abuse Act 70 of 2008. They conclude with an overview of some of the gaps in substance abuse policy in South Africa and recommendations for how these could be addressed.

Conclusion

In reviewing the list of chapters, and their contents, one cannot but be impressed by the enormity of the problem of substance use in contemporary South Africa. Substances with psychotropic effects have interwoven themselves with the social fabric of our society; they are part of everyday recreation and spiritual life, and they are a significant part of our hospitalisations, diseases, violence and 'accidents'. Given our particular context, it is not surprising that they affect particular segments of society in different ways – but it is nevertheless clear that they affect us all, black and white, male and female, young and old.

Much more needs to be done to create a critical mass of scientists and clinicians who can address problems of substance use in southern Africa. At the same time, it is heartening to see that considerable work has been initiated locally, and that there is evidence of multidisciplinary collaboration to further this work. Such work ranges from extensive epidemiological research, through to a range of brain-behaviour research, and on to sophisticated efforts to think through policies and methods for optimally preventing and treating substance use disorders.

Clearly the perspective of the editors is a multidisciplinary one, but it also frames substance use disorders as 'medical disorders', an approach in which the brain-behaviour sciences can be particularly helpful. This theoretical stance is driven by several different assumptions.

First, although there is considerable traction to be gained by understanding the molecules involved in mediating substance use disorders, human behaviour is complex, and a full understanding therefore also requires inclusion of a range of disciplines other than molecular neuroscience, ranging from neuropsychology through to clinical neuroscience, social psychology and sociology (Ellis, 2005). The key issue here is the broad nature of the intervention: does one attempt to intervene in a bottom-up way, via prescription of appropriate medication affecting neuronal function (counter-drugs will do the job!), in a

top-down way by engaging with intention and purpose (psychology and social intervention are the answer!), or in some mix of bottom-up and top-down intervention (which is probably the best). But then how does one determine what mix is most effective for whom?

Second, although substance use disorders are arguably not 'typical' medical disorders, insofar as patients suffering from these conditions might have made an initial voluntary choice to begin abusing, and bear significant responsibility for parts of their own treatment, they are nevertheless better conceptualised as medical disorders than as merely 'sinful' and 'criminal' (Stein, 2008). Once a person has initiated substance use, pathological brain changes follow, and there are medical treatments, including pharmacotherapy and psychotherapy, that are effective in dealing with these changes.

Third, and consistent with this emphasis on brain changes and clinical intervention, a perspective that includes the brain-behavioural sciences is needed for optimal understanding and management of substance use disorders. Although this may be self-evident for many readers, we feel it is important to make this explicit, given that substance abuse policies have so often ignored the insights of neuroscience and the need for clinical treatment. We hope that this volume will serve as a useful resource, not only for clinicians and researchers with an interest in substance use disorders, but also for policy-makers.

In closing, we wish to thank the contributors for their efforts. We wish to acknowledge with gratitude the University of Cape Town's support in funding the Brain-Behaviour Initiative, which provided the impetus not only for some of the research reported herein, but also for the volume itself. Finally, we wish to thank Diana Lapido Loereiro for her help in coordinating the volume.

References

Ellis, G.F. (2005). Physics, complexity and causality. *Nature*, 435 (7043):743.

Gupta, J., Silverman, J.G., Hemenway, D., Acevedo-Garcia, D., Stein, D.J. & Williams, D.R. (2008). Physical violence against intimate partners and related exposures to violence among South African men. *Canadian Medical Association Journal*, 179(6):535–41.

Kaminer, D., Stein, D.J., Mbanga, I., & Zungu-Dirwayi, N. (2001). The Truth and Reconciliation Commission in South Africa: relation to psychiatric status and forgiveness among survivors of human rights abuses. *The British Journal of Psychiatry*, 178:373–77.

Kessler, R.C., Angermeyer, M., Anthony, J.C., De Graaf, R., Demyttenaere, K., Gasquet, I., De Girolamo, G., Gluzman, S., Gureje, O., Haro, J.M., Kawakami, N., Karam, A., Levinson, D., Mora, M.E.M., Browne, M.A.O., Posada-Villa, J., Stein, D.J., Tsang, C.H.A., Aguilar-Gaxiola, S., Alonso, J., Lee, S., Heeringa, S., Pennell, B.E., Berglund, P., Gruber, M.J., Petkhova, M., Chatterji, S. & Ustun, T.B. (2007). Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry*, 6(3):168–76.

May, P.A., Gossage, J.P., Marais, A.S., Adnams, C.M., Hoyme, H.E., Jones, K.L., Robinson, L.K., Khaole, N.C., Snell, C., Kalberg, W.O., Hendricks, L., Brooke, L., Stellavato, C. & Viljoen, D.L. (2007). The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. *Drug and Alcohol Dependence*, 88(2–3):259–71.

Parry, C.D.H., Myers, B., Morojele, N.K., Flisher, A.J., Bhana, A., Donson, H. & Plüddemann, A. (2004). Trends in adolescent alcohol and other drug use: findings from three sentinel sites in South Africa (1997–2001). *Journal of Adolescence*, 27(4):429–40.

Simbayi, L.C., Kalichman, S.C., Cain, D., Cherry, C., Henda, N. & Cloete, A. (2009). Methamphetamine use and sexual risks for HIV infection in Cape Town, South Africa. *Journal of Substance Abuse*, 11(4):291–300.

Stein, D.J. (2008). *The Philosophy of Psychopharmacology: Smart Pills, Happy Pills, Pep Pills*. Cambridge: Cambridge University Press.

Van Heerden, M.S., Grimsrud, A.T., Seedat, S., Myer, L., Williams, D.R. & Stein, D.J. (2009). Patterns of substance use in South Africa: results from the South African Stress and Health study. *South African Medical Journal*, 99(5, Pt. 2):358–66.

World Health Organization. (2001). *The World Health Report 2001: Mental Health: New Understanding, New Hope*. Geneva: World Health Organization.

Epidemiology and Symptomatology

1 Epidemiology of substance use and abuse in South Africa

Shandir Ramlagan and Karl Peltzer

Introduction

At the end of the apartheid era, research relating to the nature and extent of use of drugs other than alcohol and tobacco among the general adult population in South Africa was virtually nonexistent (Rocha-Silva, 1992). In his opening address to the South African Parliament in 1994, President Nelson Mandela signalled alcohol and drug abuse as a problem among the social pathologies that needed to be combated. By February 1999, the country's Drug Advisory Board noted an unacceptable increase in substance abuse (the age of first experimentation had also dropped) and its associated problems. In 1997, the inappropriate use of narcotic drugs was estimated to cost countries between 0.5% and 1.3% of their GDP annually. In South Africa, this amounted to between R2.4 and R6.3 billion (UNODC, 2003). This problem has been identified by the National Drug Master Plan as fuelling crime, poverty, reduced productivity, unemployment, dysfunctional family life, political instability, the escalation of chronic diseases such as AIDS and TB, injury and premature death (Drug Advisory Board, 1999). Its sphere of influence reaches across social, racial, cultural, language, religious and gender barriers and, directly or indirectly, affects all South Africans.

Results and discussion

In the 1960s and 1970s, the widespread abuse of psychotropic substances emerged in South Africa. Globalisation has since facilitated the introduction of potent addictive drugs, such as heroin, cocaine and ecstasy. Leggett (2004) noted that prior to 1994, cocaine and heroin were not readily available in South Africa. After South Africa's re-integration into the world community in the 1990s, its well-developed transport and communication systems and advanced banking structure meant that the country came to be used for the purpose of illicit trafficking of many commodities, including drugs (UNOCD, 2002).

The end of apartheid has increased South Africa's vulnerability to illicit drug trafficking between source countries in Asia and South America and the major consumer markets in Western Europe and North America. While not the most direct route between these areas, South Africa may be used for trans-shipments of illegal drugs. The quality of air and sea travel connections via South Africa to many parts of the world offers drug traffickers opportunities that did not exist earlier. The country's geography, porous borders and expanding international trade links with Asia, Western Europe and North America have made it an attractive drug transit country. Drug trafficking and abuse have accordingly escalated. The point of escalation

Table 1.1: National and localised South African studies regarding substance use

AUTHOR	YEAR	ACRONYM	SCOPE	SAMPLING	SAMPLE SIZE/ AGE
Flisher et al, 1993	1993		Substance use	Cape Town secondary schools	N=7 340
Reddy et al, 1996	1995	HSRC	Tobacco	National Household Survey, multistage stratified sampling	N=2 238/16 yrs and above
Department of Health, 1998, & Steyn et al, 2002	1998	DHS	Tobacco, Alcohol	National Household Survey, multistage stratified sampling	N=13 826/15 yrs and above
Swart et al	1999	GYTS	Tobacco	National school survey	N=6 045/13–17 yrs
Visser & Moleko 1999	1999		Substance use	Pretoria primary schools	N=460
Terblanche and Venter	1999		Substance use	Port Elizabeth schools	N=382/grades 8–12
Peltzer et al, 1999	1999		Substance use	Urban secondary schools	N=191
Peltzer et al, 1999	1999		Substance use	Northern Province rural secondary schools	N=209
Reddy & Swart, 2003	2002	GYTS	Tobacco	National school survey	N=8 935/13–18 yrs
Reddy et al, 2003	2002	YRBS	Substance use	National school survey	N=10 699/13–19 yrs
Stein et al, 2009	2002–2004	SASH	Alcohol, Substance use	National Household Survey	N=4 351/18 yrs and above
Peltzer et al, 2002	2002		Substance use	University students	N=799
CASE, 2007	2003	WHS	Tobacco, Alcohol	National Household Survey, multistage stratified sampling	N=2 351/18 yrs and above
Department of Health, 2007	2003	DHS	Tobacco	National Household Survey, multistage stratified sampling	N=8 115/15 yrs and above
Flisher et al, 2003	2003		Substance use	Cape Town secondary schools	N=2 779
Plüddemann & Parry, 2003	2003		Substance use	Arrestees	N=1 000
Shisana et al	2004	HSRC	Substance use	National educator survey	N=20 626/20 yrs and above

(*continued*)

Table 1.1: National and localised South African studies regarding substance use (continued)

AUTHOR	YEAR	ACRONYM	SCOPE	SAMPLING	SAMPLE SIZE/ AGE
Mwansa et al, 2004	2004		Substance use	Bele Bele and Pretoria	N=303
Shisana et al, 2005	2005	SABSSM II	Substance use	National Household Survey, multistage stratified sampling	N=23 236/15 yrs and above
Peltzer et al, 2005	2005		Substance use	National 25 higher education 3rd/4th-year students	
Peltzer et al, 2006	2006		Substance use	Community survey	N=800
Shisana et al, 2008	2008	SABSSM III	Substance use	National Household Survey, multistage stratified sampling	N=10 828/15 yrs and above

is traceable to the fall of apartheid and the liberalisation of most aspects of society in the years following the country's first democratic elections in 1994.

Cocaine from Latin America and heroin from the Far East transits through South Africa to Europe, and the United States (US Department of State, 1996). South Africa, along with Namibia, Kenya, Swaziland, Angola, Tanzania and Uganda are now on the major cocaine trafficking routes. Colombian cocaine drug lords are reported to be moving their operations into South Africa, which allows them easier access to Europe. More recently, the cartels have established contacts with Asian and Far Eastern producers to use South Africa as a conduit for smuggling hashish, heroin and opium to Europe and the United States (Hawthorne, 1996).

Long, porous borders and weak border control, including understaffed ports and numerous secondary airports, give traffickers nearly unlimited access to South Africa. The growing presence of illicit drugs in South Africa is indirectly a result of the dramatic increase in the number of international flights to the country, relaxed visa requirements for South Africans to travel overseas, the movement of large numbers of legal and illegal people across the borders, poor border monitoring and ill-equipped customs officials. All of these create a highly attractive market for the influx of drugs (SAPA, 1995), and a growing reputation as a 'paradise' emerging market and transit point for illicit drugs (Steyn, 1996; Ryan, 1997). Although there is little available evidence to substantiate it, the growth of organised crime, and the lack of adequate resources to deal with it contributes, among other factors, to an increase in the accessibility and availability of illicit drugs in South Africa. A corresponding increase in consumption is probable.

Tobacco use and abuse

According to the World Health Organization (Saloojee, 2006), 4 million deaths worldwide are attributed to tobacco each year. In South Africa, according to Groenewald (2007),

34 108 deaths in males (12.4% of all male deaths) and 10 306 deaths in females (4.2% of all female deaths) in 2000 were attributed to tobacco. The tobacco-related studies in Table 1.2 show that from 1999 (Global Youth Tobacco Survey, or GYTS) to 2002 (GYTS) the percentage of children below 10 years of age who had started using tobacco among those with a history of having smoked seemed to have decreased from 18% to 16%. In Table 1.2, from 1999 to 2002, we also see that there seems to be a decline among adolescents in lifetime tobacco use from 46.7% to 37.6% (GYTS, 2002) to 30.5% (Youth Risk Behaviour Survey, or YRBS, 2002). Current tobacco use among adolescents also seems to be declining, yet at a smaller rate, from 23% (GYTS, 1999) to 18.5% (GYTS, 2002), with YRBS in 2002 reporting 21.1%. Although there is a relatively high proportion of smokeless tobacco use among adolescents, (18% to 21%), there seems to be a decline in its use from 18% (GYTS, 1999) to 15% (GYTS, 2002), with YRBS (2002) reporting 11%. The 1998 Demographic Health Survey (DHS) and the GYTS (1999) showed daily smoking among adolescents at 10.6% and 10.1%, respectively. The GYTS (2002) and YRBS (2002) figures indicate a decline to 5.8% and 6.5%, respectively.

Surveys of South African adult smoking trends (see Table 1.3) show that daily smoking declined from 26.2% in 1998 (DHS) to 19.8% in 2003 (DHS), with the World Health Survey (WHS, 2003) reporting 14.6%. Among a national sample of educators (HSRC, 2004), daily smoking was reported by 8.5% of educators. Daily tobacco use was found in four national surveys to be higher among urban than rural residents, higher in the Western Cape and Northern Cape than in other provinces, higher among coloureds, whites and Indians than Africans, and higher among those with a lower education level.

Alcohol use and abuse

Globally, the net effect of alcohol consumption on health is detrimental, with an estimated 3.8% of all global deaths and 4.6% of global disability-adjusted life-years (DALYs) attributable to alcohol (Rehm et al, 2009). In South Africa, the estimated burden of disease attributable to alcohol use in 2000 was estimated at 7.1% (95%, uncertainty interval 6.6–7.5%) of all deaths and 7.0% (95%, uncertainty interval 6.6–7.4%) of total DALYs. As a cause of alcohol-attributable disability, alcohol use disorders ranked first (44.6%), interpersonal violence second (23.2%), and fetal alcohol syndrome (FAS) third (18.1%) (Schneider et al, 2007).

How alcohol is consumed in a country or within a group (ie, pattern of drinking) is an important determinant of types and levels of problems associated with drinking. Alcohol consumption should be understood in the context of how it is drunk, that is, the patterns of drinking. Hazardous drinking is defined as a quantity or pattern of alcohol consumption that places patients at risk for adverse health events, while harmful drinking is defined as alcohol consumption that results in adverse events (e.g. physical or psychological harm) (Reid et al, 1999).

In 2005, the second South African National HIV Prevalence, HIV Incidence, Behaviour and Communication Survey (SABSSM II) showed a decline in lifetime and current alcohol use among adolescents, whereas the 2008 survey (SABSSM III) survey showed a slight increase (see Table 1.4). Lifetime and current alcohol use among adults seemed to have remained stable for the adult population (Peltzer & Ramlagan, 2009). Current (past month)

Table 1.2: Adolescent tobacco use status (more harmful) by age and sex

	1998 DHS (15–19 yrs; N=2 249)		1999 GYTS (13–17 yrs; N=6 045)		2002 GYTS (13–18 yrs; N=8 935)		2002 YRBS (13–19 yrs; N=10 699)	
	Tobacco products		Cigarettes (other tobacco products)		Cigarettes (other tobacco products)		Cigarettes (other tobacco products)	
Ever used	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Initiation age <10			18.9*	17.7*	16.5*	16.4*	8.7	4.2
≤13			50.9	37.3	45.2	20.5	26.4	17.1
14			41.9	37.3	40.4	31.9	35.2	24.6
15	6.3	5.4	60.6	41.2	46.9	35.4	37.0	27.2
16	15.0	5.4	58.2	40.4	47.1	31.4	42.9	28.8
17	17.0	7.8	59.4	35.1	53.6	20.7	47.5	20.2
18	21.8				50.3	22.4	41.3	14.0
19	25.0						38.2	14.7
Total	16.8	9.2	56.4	38.8	47.6	28.8	40.0	23.0
Overall total	13.0		46.7		37.6		30.5	
Current smoking	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
≤13			26.8(27.3)	15.7(23.9)	18.9(8.1)	5.3(7.3)	15.2(7.3)	9.0(18.6)
14			16.6(17.6)	17.9(9.3)	18.9(12.7)	10.3(11.2)	21.5(9.7)	15.7(9.0)
15	4.1	2.4	21.3(15.0)	16.5(11.8)	23.4(18.0)	13.6(15.0)	27.6(9.2)	17.0(7.7)
16	10.2	3.2	31.0(16.0)	20.1(12.3)	24.9(12.3)	13.2(11.1)	30.4(10.4)	19.2(7.9)
17	14.6	5.0	38.2(24.1)	17.3(22.7)	36.3(17.7)	11.7(16.3)	33.0(10.8)	14.9(8.4)
18	20.0	9.2			34.2(18.4)	13.6(18.2)	38.2(13.9)	12.2(13.0)
19	22.4	9.5					33.5(13.1)	9.4(13.2)
Total	14.0	5.7	28.8(19.9)	17.5(15.0)	26.8(15.9)	11.5(13.1)	29.0(10.8)	14.9(10.5)
Overall total	10.5		23.0(18.2)		18.5(14.5)		21.1(10.5)	
Daily use**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
≤13			11.3	7.9	6.2	1.1	3.2	1.4
14			6.7	5.0	6.0	1.5	4.3	2.6
15	2.8	1.6	6.4	6.6	8.2	3.6	7.5	4.8
16	8.9	2.7	13.7	13.0	7.3	3.5	10.7	6.0
17	10.3	2.8	25.2	10.2	13.7	2.5	11.9	3.6
18	17.0	8.5			14.0	3.3	18.8	3.6

(*continued*)

Table 1.2: Adolescent tobacco use status (more harmful) by age and sex (continued)

	1998 DHS (15–19 yrs; N=2 249)		1999 GYTS (13–17 yrs; N=6 045)		2002 GYTS (13–18 yrs; N=8 935)		2002 YRBS (13–19 yrs; N=10 699)	
	Tobacco products		Cigarettes (other tobacco products)		Cigarettes (other tobacco products)		Cigarettes (other tobacco products)	
Daily use**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
19	17.4	6.9					12.3	1.2
Total	16.8	4.4	15.1	8.7	9.5	2.7	10.0	3.7
Overall total	10.6	10.1	5.8	6.5				

*Among those with a history of having smoked
**20 or more in past month
Source: Table adapted from Peltzer (2008).

Table 1.3: Adult tobacco use status (more harmful) by age and sex

	1998 DHS		2003 DHS (2003 WHS)		2004 HSRC Educators	
	Daily smoking		Daily smoking		Daily smoking	
Ever used	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
15–24	20	4.7	20.5	6.7		
25–34	45.1	6.5	37.3	5.5	17.1	3.1
35–44	51.1	14.6	41.3	12.5	19.5	3.3
45–54	44.3	15.3	41.3	12.2	19.7	5.7
55–64	39.8	9.3	31.1	12.6	21.3	5.1
65+	35.4	6.6	25.3	6.1		
Total	42.0	11.0	31.7(22.2)	9.0(7.0)	18.8	4.0
Overall total	26.2		19.8(14.6)		8.5	

Source: Peltzer (2008)

alcohol use has been about 30% (40% among men and 16% among women), which is lower than the levels reported for other developing countries, e.g. Namibia (men 61%, women 47%), Mexico (men 77%, women 44%) and Thailand (men 77%, women 46%) (Room et al, 2002).

The 2008 SABSSM III rates show a slight increase compared with SABSSM II, 2005, with 24.5% overall, and 39.2% for men and 15.7% for women. However, these levels were about the same in the DHS of 1998, with 28% overall; 44.6% and 16.9% current drinkers among men and women, respectively.

Binge drinking among youth (15–24 years) increased slightly, from 29% of current drinkers in 1998 (DHS) to 31% of current drinkers in 2005 (SABSSM II). Among adults,

Table 1.4: Current (past month) alcohol use

	1998 DHS*		2005 SABSSM II* (WHS 2003)		2008 SABSSM III**		2002 YRBS*	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Age								
15–19	25.3	14.7	17.2	8.4	21.5	9.4	38.5	26.6
20–24			42.0	14.6	41.2	12.9		
15–24	23.3	8.5	27.6	11.6				
25–34	51.7	15.6	45.2	13.9	47.6	20.5		
35–44	58.9	20.9	49.7	17.4	52.4	21.4		
45–54	60.0	23.4	53.2	22.5	49.5	20.0		
55–64	54.2	20.5	46.4	20.8	44.6	16.6		
65+	45.7	20.3	34.9	14.4	34.6	11.6		
Total	44.6	16.9	39.2(41.3)	15.7(16.7)	41.5	17.1		
Overall total	28.0		24.5(29.9)		27.7		31.8	

*Peltzer & Ramlagan, 2009
**Peltzer, Davids & Njuho (in print)

binge drinking was relatively high: 32.4% for women in 1998 (DHS), compared to 20.6% among female current drinkers in the 2005 survey. The SABSSM III study found that overall 9.6% of South Africans (17.1% among men and 3.8% among women) engaged in past-month binge drinking (Peltzer et al, submitted). These rates also show a slight increase compared with SABSSM II, with 7.4% overall, and 14.3% in men and 3.2% in women (Peltzer & Ramlagan, 2009).

Among youth (15–24 years), problem drinking with the CAGE (Cut down, Annoyed, Guilty, Eye-opener) assessment measure (see Chapter 2 for more details) was 17% among men and 6% among women in 1998 (DHS). Hazardous or harmful drinking assessed with the AUDIT (Alcohol Use Disorder Identification Test) measure (see Chapter 3 for more details) was 10% among men and 2% among women in the same age group in 2005 (SABSSM II). Among adults, 17% were problem drinkers (assessed with the CAGE) in 1998, 6% (assessed with the AUDIT) in 2005 and 5% (assessed with the AUDIT) among a large representative sample of educators in 2004. Further, the 2008 SABSSM III study found that hazardous or harmful alcohol use was 9.0% (in men 17% and women 2.9%), which is a considerable increase from SABSSM II 2005, with an overall rate of 6.2%; in men 12.7% and women 2.2% (Peltzer & Ramlagan, 2009). This is, however, still lower than in other developing countries: for example, in Tibet the overall figure is 16.2% (female 9.6%, male 31.6%) (Guo et al, 2008); in rural Vietnam it is 25.5% among men and 0.7% among women (Giang et al, 2008); among 16–25-year-olds in Thailand, the figure for hazardous and harmful drinking is 24.3% (Jirapramukpitak et al, 2008). This is lower than in European Union countries,

where the comparable figure is 15% (Anderson et al, 2006), and similar to Sweden, where 18% of men and 5% of women reported hazardous or harmful alcohol use (Bergman et al, 2002).

In South Africa, higher binge drinking levels were found in urban than in rural areas among men (17% and 11%, respectively) and women (4% and 2%, respectively) in SABSSM II (2005) and in the WHS (12% and 9%, respectively). However, among current drinkers higher levels of binge drinking were found among rural than urban women in both DHS (1998) (39% and 29%, respectively) and SABSSM II (26% and 19%, respectively).

According to province, SABSSM II showed that the highest rates of binge drinkers among men were in the Western Cape (24%), followed by North West (20%), Gauteng (16%) and Free State (15%). According to racial group, SABSSM II showed that binge drinking among men was highest among coloureds (23%), followed by whites (16%), blacks (13%) and Indians or Asians (7%). However, among male current drinkers the highest levels of binge drinking were found among coloureds (41%) and blacks (41%), as opposed to whites (25%) and Indians or Asians (18%). Both the DHS 1998 and SABSSM II showed that lower levels of education were associated with higher levels of binge drinking among current drinkers. These findings are similar to that of the SABSSM III survey (Peltzer at al, submitted).

Cannabis use and abuse

South Africa is a major producer of cannabis (the world's third largest), most of which is consumed in the southern African region, but at least some of which finds its way to Europe (UNODC, 2006). Cannabis is cultivated in South Africa, but is also imported from neighbouring countries (Swaziland, Lesotho, Mozambique, Zimbabwe), exported to some of the neighbouring countries (eg, Namibia) and Europe (mainly the Netherlands and the UK) and, of course, consumed in South Africa (Peltzer & Ramlagan, 2007). According to Parry and Bennets (1998), cannabis comes second to alcohol as the most extensively used drug in South Africa.

The school-based Youth Risk and Behaviour Survey (YRBS) conducted in 2002 in South Africa (Reddy et al, 2003) found that current (past month) use of cannabis was 9% among students (see Table 1.5). Table 1.5 also shows that between 2005 and 2008, according to the SABSSM II and SABSSM III surveys, cannabis usage almost doubled in all categories.

Higher current cannabis use rates were found in urban (2.3%) than in rural (1.0%) areas in both SABSSM II and SABSSM III surveys. According to Peltzer et al (in press), among school students current cannabis use was highest in the provinces of Gauteng, Western Cape, Mpumalanga, Free State and Limpopo. The highest rates among adults were in Western Cape, Gauteng and North West. Among adolescents, current cannabis use was highest among Indians or Asians and coloureds, while among adults it was highest among coloureds and whites. Current cannabis use was especially low (about 0.2% or less) among women from black African and Indian/Asian backgrounds. Current cannabis use rates seem not to be related to any educational level.

Table 1.5: Current cannabis use

	2002 YRBS* (13–19 yrs; N=10 699)		2005 SABSSM II* (15 years and above; N=23 236)			2008 SABSSM III** (15 years and above; N=13 828)		
	Men	**Women**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
Age group								
13–19	13.7	5.5						
	9.1							
15–19 years			2.5	1.1	1.7	4.5	1.5	3.2
20 and above			4.4	0.3	1.7			
15 and above						6.1	1.2	3.3
Geotype								
Urban			4.7	0.7	2.3	6.7	1.5	3.8
Rural			2.7	0.0	1.0	5.1	0.6	2.5
Province								
Western Cape (WC)	17.0	6.7	6.8	1.5	3.6	11.7	2.0	6.7
Eastern Cape (EC)	11.3	2.7	2.5	0.2	1.0	4.2	1.0	2.4
Northern Cape (NC)	10.0	2.6	3.1	0.3	1.3	10.6	1.2	5.6
Free State (FS)	15.6	4.0	3.3	0.2	1.4	10.6	0.1	4.9
KwaZulu-Natal (KZN)	13.6	4.4	3.3	0.1	1.2	4.1	1.9	2.7
North West (NW)	11.1	5.0	4.3	0.0	1.7	6.8	0.1	3.1
Gauteng (GP)	18.3	6.2	5.5	0.8	2.9	4.2	1.6	2.8
Mpumalanga (MP)	14.1	7.7	2.1	0.3	1.1	5.6	0.5	2.7
Limpopo (LP)	10.2	8.7	2.0	0.0	0.7	5.6	0.1	2.5
Population group								
Black African	13.4	5.3	3.5	0.1	1.4	5.5	0.8	2.8
Coloured	16.2	8.3	5.8	1.3	3.1	14.3	2.7	8.4
White	10.2	5.3	4.9	1.3	2.8	4.0	3.2	3.5
Indian/Asian	25.3	7.4	1.1	0.1	0.6	2.2	0.6	1.3
Education								
No education			4.1	0.0	1.2	6.4	0.4	2.3
Gr 1–5			4.7	0.1	1.8	9.5	0.7	4.5
Gr 6–7			4.3	0.2	1.7	10.1	0.8	5.0
Gr 8–11	13.7	5.5	3.7	0.4	1.7	5.7	1.1	3.2
Gr 12			4.8	0.9	2.3	4.6	1.6	2.9
Higher			2.2	0.2	1.1	4.5	1.6	2.9

*Peltzer, Ramlagan, Johnson & Phaswana-Mafuya (in print)
**Peltzer & Ramlagan (in print)

The range of current use of cannabis among adolescents is from 2% to 9% in three national samples (YRBS, SABSSM II and SABSSM III).

Treatment demand for cannabis abuse alone increased from 14% in 1999 to 17% in 2005 of all treatment demand, while treatment for cannabis mixed with Mandrax has remained stable: 7% in 1999 and 7% in 2005 of treatment demand of all drugs (Peltzer & Ramlagan, 2007). From 1999 to 2005, cannabis treatment demand has been consistently the highest in treatment centres in KwaZulu-Natal (see Figure 1.1) and cannabis and Mandrax treatment demand has been consistently the highest in treatment centres in the Eastern Cape. In South Africa, as in other countries, there has been an increase in the share of primary cannabis users in treatment populations since 2002: Denmark (27%), Greece (7%), Netherlands (17%) and UK (10%) (Peltzer & Ramlagan, 2007).

Other illicit drugs

Based on four national surveys among adolescents (see Table 1.6), lifetime illicit drug use was highest for over-the-counter or prescription drugs (16%), followed by inhalants (0.2–11.1%), cocaine (crack) (0.1–6.4%), Mandrax/sedatives (0.1–6.4%), club drugs (0.2–5.8%) and opiates (11.5%). (The latter figure, from the 2002 YRBS, seems unreasonably high.) Past-three-month use appears to be well under 1% for most of these drugs in general population samples. Less than 0.3% of adult females reported past-three-month use of each non-cannabis drug. There were gender differences: more male than female adolescents took inhalants, Mandrax/sedatives, club drugs and cocaine (crack) (see Table 1.6).

Drug treatment demand

Drug treatment data provide information about those seeking help. The primary substance(s) of abuse at admission to most government-funded treatment centres (n=60) in 2006 in South Africa was alcohol (51.3%), cannabis (19.9%), methamphetamine (tik) (5.2%), crack/cocaine (7.8%), cannabis and Mandrax (2.6%), heroin/opiates (5.5%) and prescription and OTC (2.8%) (Peltzer et al, in print). Treatment admissions were concentrated in the most populated provinces: Gauteng (37.9%), Western Cape (32.3%), Eastern Cape (9.4%), Mpumalanga (6.1%) and KwaZulu-Natal (5.9%). Treatment demand was overrepresented for men (79.3%) as opposed to women (20.3%). Whites (38.7%) and coloureds (30.8%) were overrepresented, compared with blacks (27.4%) and Indian or Asians (3.0%). There has also been a steady increase in treatment demand for young people (below 20 or 22 years), who now constitute 26.7% of the treatment demand (see Table 1.7).

Overall, the number of treatment admissions has significantly increased over the past 10 years. The percentage of admissions for cannabis, heroin and methamphetamine increased between 1996 and 2005, while the admission percentages decreased for alcohol. Cannabis abuse alone increased from 14% in 1999 to 17% in 2005 of all treatment demand. The figure for cannabis mixed with Mandrax has remained stable from 7% in 1999 to 7% in 2005 (see Figure 1.2).

There has been an increase in demand for drug treatment by young persons under 20 years of age. For example, from January 1997 to December 2001 treatment demand

Table 1.6: Other illicit drugs status by age and gender among youths in South Africa

	1994 HSRC*	**2002 YRBS***		**2005 SABSSM II***		**2008 SABSSM III****
	(10–21 yrs)	**(13–19 yrs)**		**15–19 yrs (20 above)**		**15–19 yrs (15 and above)**
	Black African					
Usage	**Ever used**	**Ever used**		**Past 3 months**		**Past 3 months**
		Men	**Women**	**Men**	**Women**	
Inhalants (glue, petrol, paint thinner, etc.)		13.1	9.5	0.4 (0.2)	0.0 (0.0)	
Total		11.1		0.2 (01)		0.8 (0.5)
Mandrax, sedatives		7.6	4.8	0.2 (0.6)	0.1 (0.1)	
Total	1.9	6.0		0.1 (0.3)		0.7 (0.8)
Cocaine (crack)		7.3	5.6	0.2 (0.5)	0.0 (0.2)	
Total	0.9	6.4		0.1 (0.3)		0.7 (0.6)
Opiates (heroin, morphine, Welconal, etc.)		11.8	11.3	0.0 (0.2)	0.0 (0.0)	
Total	3.0	11.5		0.0 (0.1)		0.7 (0.5)
Club drugs/ amphetamine-type stimulants (speed, ecstasy, tik, etc.)		7.6	4.4	0.2 (0.4)	0.2 (0.1)	
Total	2.0	5.8		0.2 (0.2)		0.8 (0.7)
Hallucinogens (LSD, etc.)			0.0 (0.3)	0.2 (0.0)		
Total	1.9			0.1 (0.1)	0.7 (0.5)	
Over-the-counter or prescription drugs		16.4	14.8			
Total		15.5				

*Peltzer, Ramlagan, Johnson & Phaswana-Mafuya (in print)
**Peltzer & Ramlagan (submitted)

for heroin-related problems increased from 2.1% to 9.1%, and ranged between 0.0% and 14.3% of the total number of adolescents in substance abuse treatment in Gauteng, Cape Town and Durban, respectively (Parry et al, 2004). In Cape Town, the proportion of black African patients having cocaine as a primary drug of abuse has been consistently low (under

Table 1.7: Treatment demand by province and by gender, race, age and primary drug of abuse, as percentage (2006)

IN-/ OUTPATIENTS	EC	KZN	WC	GP	MP	LP	FS	NC	NW	TOTAL
Number	1 395	1 428	5 458	6 414	1 040	74	544	342	291	16 986
Male	84.0	84.5	74.5	80.5	83.5	78	81.5	84.5	77.5	80.9
Black African	35.5	39	6.5	35	50.5	46	33.5	30	28	33.8
Coloured	32.5	10.5	68	10	4	4	13	55.5	4	22.4
White	29.25	25.5	24	52	22.5	50	52.5	12.5	67.5	37.3
Indian/Asian	2.75	25	1	3	23	0	<1	1.5	1	6.4
<20 *<22	17	25	27	23	18.5	26*	20.5*	40*	11*	23.1
20–34 #22–35	44.7	35.5	46.5	38	42	24#	33#	27#	37.5#	36.5
35–49	29.0	29.5	21	27.5	29	0	19	10.5	18	20.4
50–64 **50+	7.0	10**	6	10.5	9.5	45	9	5	10	12.4
65+	<1	0	1	<1	<1	5	<1	1	3	1.1
Alcohol	46.5	43	28	48	51	57	61	57.5	69.5	51.3
Cannabis	18.3	26	9	21	29.5	23	22	22	8.5	19.9
Cannabis/Mandrax	5.75	2	3	2	<1	0	1.5	5	4	2.6
Crack/cocaine	15.3	11.5	4.5	11	6	1	8.5	1.5	10.5	7.8
Heroin/opiates	3.8	5	12	9	10	3	2	2	3	5.5
Prescription/OTC	2.5	7	1.5	3	2	3	4	1	1.5	2.8
Methamphetamine	2.5	0	39.5	<1	0	0	0.2	0.5	4.5	5.2

EC to MP Jan–Dec 2006 (Source: SACENDU); FS to NC Apr–Sept 2006 (Source: SANCA) and July–Dec 2006 (Source: SACENDU); Italic data July–Dec 2006 (Source: SACENDU); * <22 years old; # 22–35 years old; ** 50+ years old
Source: Peltzer, Ramlagan, Johnson & Phaswana-Mafuya (in print)

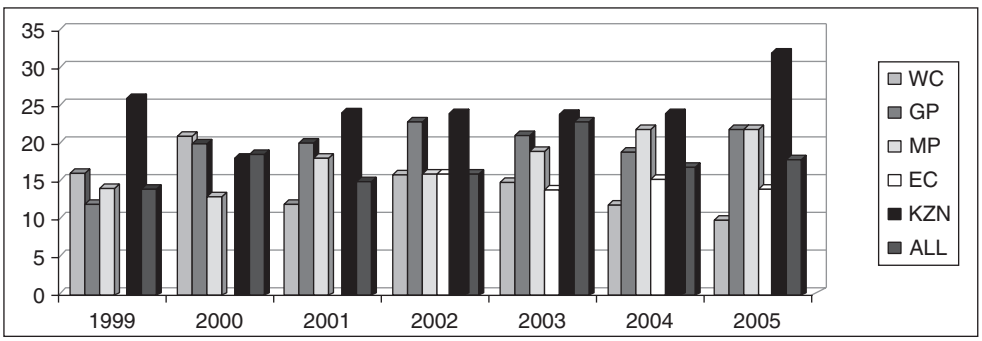

Figure 1.1: Percentage of all treatment demand for cannabis as primary drug
Source: SACENDU

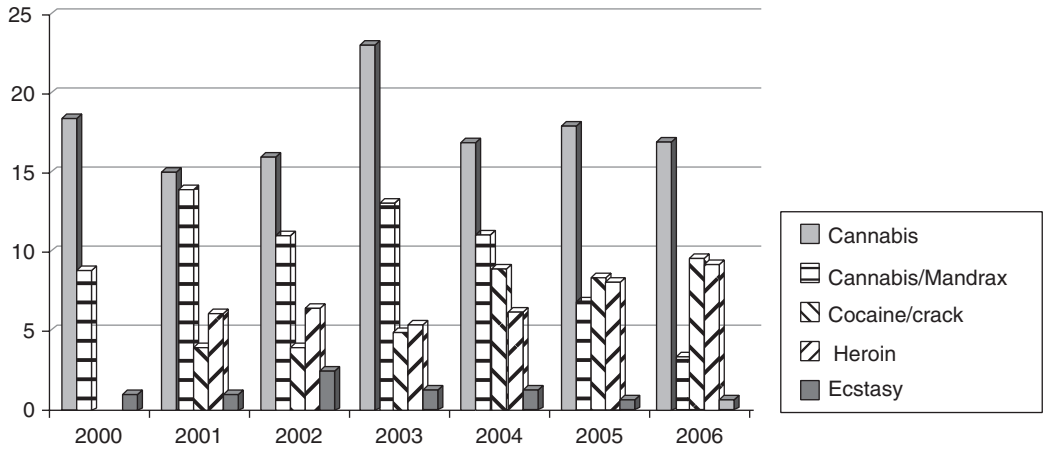

Figure 1.2: Percentage of all treatment demand for illicit primary drugs in South Africa*
*SACENDU and SANCA (2000–2005 SACENDU: five provinces; 2006 SACENDU & SANCA: all nine provinces)

Source: Peltzer, Ramlagan, Johnson & Phaswana-Mafuya (in print)

7%), whereas there has been an increase in the proportion of cocaine patients who are coloured, from 3.6% in 1997 to 31.1% in 2006. The latter has resulted from a decline in the proportion of cocaine patients who are white (Parry, Plüddemann & Myers, 2007). In Gauteng, between 1999 and 2006 roughly 60% or more patients having cocaine as a primary drug of abuse were white. The proportion of patients treated for a cocaine-related problem who were black African in Gauteng increased significantly from 4.8% in the second half of 1999 to 12.5% in the second half of 2006. Parry et al (2007) also conducted a Cochrane-Armitage trend test with SACENDU data from 1997 to 2006, and found that the proportion of patients in Gauteng, Cape Town and the Eastern Cape reporting cocaine as their primary drug of abuse, relative to other substances, increased significantly in all sites over time. Similarly, there was a significant increase in the proportion of cocaine patients who were coloured, from 8.8% to 18.7% (Parry et al, 2007). In Gauteng, between 1998 and 2003 consistently almost 90% of heroin patients were white, and in Cape Town the corresponding percentage was about 80%; the range for blacks was 0–7% in Gauteng and 0–6% in Cape Town, and for coloureds was 0–2% in Gauteng and 2–32% in Cape Town (Parry, Plüddemann & Myers, 2005).

Conclusion

It is encouraging to state that overall tobacco use seems to be on the decline, probably due to policy and pricing (taxation) of tobacco products. Peltzer (2008) quotes Van Walbeek (2005) in showing that the rapid increase in excise taxes raised the real (inflation-adjusted) price of cigarettes by 115% between 1993 and 2003, in turn decreasing the aggregate consumption of cigarettes by about a third. Legislation such as the banning of tobacco advertising and sponsorship, and the prohibition of smoking in public places, is also

believed to have decreased tobacco consumption. Although all this is very good news, at the current prevalence rates tobacco's addition to South Africa's burden of disease will still be high.

The proportion of the population consuming alcohol in South Africa is low compared to other countries. However, many of those who drink appear to engage in risky drinking regularly, so that South Africa has one of the highest rates of alcohol use disorders in the world (Kessler et al, 2007). Over the years, the lifetime and current consumption trends seem to remain stable. However, there is also evidence of increased alcohol use in younger cohorts (see also Chapter 13), as well as increases in binge drinking. The use of alcohol and substances by pregnant women, and the consequent high prevalence of fetal alcohol syndrome, is particularly worrying (see Chapters 3 and 4). Thus there is a need to develop and implement a comprehensive strategy to curb the misuse of alcohol in South Africa (Parry et al, 2005) (see also Chapter 19).

Cannabis is the most common illicit substance used in South Africa, in keeping with world trends, with use being particularly high among the youth. Available data seem to point to cannabis use increasing, especially if one looks at the treatment-demand data. Cannabis is readily available and cheap to acquire. Increasing cannabis usage also increases its burden of disease. Similarly, the increase in methamphetamine usage has been accompanied by a particular increase in psychotic illness presenting for care. Such increases in treatment demand have implications for the already burdened healthcare system and specialist treatment facilities (see Chapter 18 for more on the treatment gap in South Africa).

The prevalence rates of illicit drug use in South Africa are moderately high; they are lower than those in some other countries such as the United States and Australia, but higher than in many other countries (Degenhard et al, 2010). Two optimistic findings are worthy of special mention. First, South Africa's largest population, black Africans, appear to have among the lowest prevalence rates of illegal drugs other than cannabis. Even for cannabis, however, prevalence rates of use among blacks are lower than among whites and coloureds. Second, the self-reported use of every illegal drug in epidemiological surveys cited above appears to be lower and often substantially lower (often by half) than the prevalence rates reported in comparable population surveys in the United States and Australia. Of increasing concern, however, is that the age of initiation for drug use appears to be decreasing (see also Chapter 13). It is notable that, in South Africa, cannabis may quite often be used even before tobacco or alcohol (Degenhardt et al, 2010).

Despite all the data reviewed above, much additional information is needed to monitor the long-range trends more systematically, and especially to provide improved data at the local level. A problem with South African studies is that they use different methodologies, different sampling frames and take place over different periods, but, according to Saloojee (2006), when looked at as a whole, they do provide useful information regarding trends. What is required is a dedicated national household survey on substance use and health (including treatment need) for persons 12 years and above. This survey should occur every three years, to monitor substance use trends in South Africa.

References

Anderson, P. & Baumberg, B. (2006). *Alcohol in Europe*. London: Institute of Alcohol Studies.

Bergman, H. & Källmén, H. (2002). Alcohol use among Swedes and a psychometric evaluation of the alcohol use disorders identification test. *Alcohol and Alcoholism*, 37(3):245–51.

Community Agency for Social Enquiry (CASE). (2007). *World Health Survey 2003: Report of South Africa*. Geneva: World Health Organization.

Degenhardt, L., Dierker, L., Chiu, W.T., Medina-Mora, M.E., Neumark, Y., Sampson, N., Alonso, J., Angermeyer, M., Anthony, J.C., Bruffaerts, R., de Girolamo, G., de Graaf, R., Gureje, O., Karam, A.N., Kostyuchenko, S., Lee, S., Lépine, J.P., Levinson, D., Nakamura, Y., Posada-Villa, J., Stein, D., Wells, J.E. & Kessler, R.C. (2010). Evaluating the drug use 'gateway' theory using cross-national data: consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. *Drug and Alcohol Dependence*, 108:84–97.

Department of Health. (1998). *South African Demographic and Health Survey 1998*. Pretoria: Department of Health.

Department of Health. (2007). *South African Demographic and Health Survey 2003*. Pretoria: Department of Health.

Drug Advisory Board. (1999). *National Drug Master Plan*. Cape Town: Department of Welfare.

Flisher, A.J., Parry, C.D.H., Evans, J., Muller, M. & Lombard, C. (2003). Substance use by adolescents in Cape Town: prevalence and correlates. *Journal of Adolescent Health*, 32:58–65.

Flisher, A.J., Ziervogel, C.F., Chalton, D.O., Leger, P.H. & Robertson, B.A. (1993). Risk-taking behaviour of Cape Peninsula high-school students. Part V. Drug use. *South African Medical Journal*, 83(7):483–85.

Giang, K.B., Allebeck, P., Spak, F., Van Minh, H. & Dzung T.V. (2008). Alcohol use and alcohol consumption-related problems in rural Vietnam: an epidemiological survey using AUDIT. *Substance Use & Misuse*, 43(3–4):481–95.

Groenewald, P., Vos, T,, Norman, R., Laubscher, R., Van Walbeek, C., Saloojee, Y., Sitas, F. & Bradshaw, D.; South African Comparative Risk Assessment Collaborating Group. (2007). Estimating the burden of disease attributable to smoking in South Africa in 2000. *South African Medical Journal*, 97(8):674–81.

Guo, W., Lanzi, G., Luobu, O., Ma, X., Zhen, P., Ji, Y., Wei, G., Wang, Z., Deng, W., Zhuoma, B., Wang, Y., Shi, X., Yan, C., Liu, X., Collier, D.A., Ball, D. & Li, T. (2008). An epidemiological survey of alcohol use disorders in a Tibetan population. *Psychiatry Research*, 159(1–2):56–66.

Hawthorne P. (1996). Cocaine's new conduit. *Time*, 9 December.

Jirapramukpitak, T., Prince, M. & Harpham, T. (2008). Rural-urban migration, illicit drug use and hazardous/harmful drinking in the young Thai population. *Addiction*, 103(1):91–100.

Leggett, T. (2002). *Drugs and crime in South Africa: a study in three cities*. Monograph 69. Pretoria: Institute for Security Studies.

Mandela, N. (1994). Opening address to the South African Parliament. Pretoria: Office of the President.

Mwansa, A.N., Rocha-Silva, L., Saxena, S., Mbatia, J., Ndubani, P. & Weir-Smith, G. (2004). Psychoactive substance use among young people: findings of a multi-centre study in three African countries. *Contemporary Drug Problems*, 31(2):329–56.

Parry, C.D.H. & Bennets, A.L. (1998). *Alcohol Policy and Public Health in South Africa.* New York: Oxford University Press.

Parry, C.D.H., Myers, B., Morojele, N.K., Flisher, A.J., Bhana, A., Donson, H. & Plüddemann, A. (2004). Trends in adolescent alcohol and other drug use: findings from three sentinel sites in South Africa (1997–2001). *Journal of Adolescence*, 27:429–40.

Parry, C.D.H., Plüddemann, A. & Myers, B.J. (2005). Heroin treatment demand in South Africa: trends from two large metropolitan sites (January 1997–December 2003). *Drug and Alcohol Review*, 24:419–23.

Parry, C.D.H., Plüddemann, A. & Myers, B.J. (2007). Cocaine treatment admissions at three sentinel sites in South Africa (1997–2006): findings and implications for policy, practice and research. *Substance Abuse Treatment, Prevention, and Policy*, 2:37.

Peltzer, K. (2008). Tobacco use trends among adolescents and adults in South Africa. *Journal of Psychology in Africa*, 18(2):339–46.

Peltzer, K., Cherian. V.I. & Cherian, L. (1999a). Substance use among rural secondary school pupils in the Northern Province, South Africa. *Journal of Psychology in Africa*, 9(1):58–65.

Peltzer, K., Cherian. V.I. & Cherian, L. (1999b). Substance use among urban secondary school pupils in South Africa. *Southern African Journal of Child & Adolescent Mental Health*, 11(1):49–55.

Peltzer, K., Davids, A. & Njuho, P. (2011). Alcohol use and problem drinking in South Africa: findings from a national population-based survey in 2008. *African Journal of Psychiatry,* 14:30–37.

Peltzer, K., Malaka, D.W. & Phaswana, N. (2002). Prevalence of substance use among first-year university students in South Africa: baseline assessment for primary prevention intervention. *The Social Work Practitioner Researcher*, 14(1):67–79.

Peltzer, K., Promtussananon, S., Mashego, T-A.B. (2006). *Youth Sexuality in the Context of HIV/AIDS in South Africa*. New York: Nova Publishers.

Peltzer, K. & Ramlagan, S. (2007). Cannabis use trends in South Africa. *South African Journal of Psychiatry*, 13(4):126–31.

Peltzer, K. & Ramlagan, S. (2009). Alcohol use trends in South Africa. *Journal of Social Science*, 18(1):1–12.

Peltzer, K. & Ramlagan, S. (2010). Illicit drug use in South Africa: findings from a national population based survey in 2008. *South African Journal of Psychiatry,* 15(4):93–100.

Peltzer, K., Ramlagan, S., Johnson, B.D. & Phaswana-Mafuya, N. (2010). Illicit drug use and treatment in South Africa: a review. *Substance Use and Misuse,* 45:2221–43.

Peltzer, K., Shisana, O., Udjo, E., Wilson, D., Rehle, T., Commolly, C., Zuma, K., Letlapa, L., Louw, J., Simbayi, L., Zungu-Dirwayi, N., Ramlagan, S., Magome, K., Hall, E. & Phurutse, M. (2005). *Educator Supply and Demand in the South African Public Education System: Integrated Report*. Cape Town: HSRC Press.

Plüddemann, A, & Parry, C.D.H. (2003). A short report: self-reported drug use vs. urinalysis in a sample of arrestees in South Africa. *Drugs: Education, Prevention and Policy*, 10(4):379–83.

Ramlagan, S., Peltzer, K. & Matseke, G. (2010). Epidemiology of drug abuse treatment in South Africa. *South African Journal of Psychiatry*, 16(2):40–49.

Reddy, P., Meyer-Weitz, A. & Yach, D. (1996). Smoking status, knowledge of health effects and attitudes towards tobacco control in South Africa. *South African Medical Journal*, 86:1389–93.

Reddy, P. & Swart, D. (2003). *Preliminary Report on the Global Youth Tobacco Survey, 2002*. Cape Town: Medical Research Council.

Reddy, S.P., Panday, S., Swart, D., Jinabhai, C.C., Amosun, S.L., James, S., Monyeki, K.D., Stevens, G., Morejele, N., Kambaran, N.S., Omardien, R.G., & Van den Borne, H.W. (2003). *Umthenthe Uhlaba Usamila – The 1st South African Youth Risk Behaviour Survey 2002*. Cape Town: South African Medical Research Council.

Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y. & Patra, J. (2009). Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet*, 373(9682):2223–33.

Reid, M.C., Fiellin, D.A. & O'Connor, P.G. (1999). Hazardous and harmful alcohol consumption in primary care. *Archives of Internal Medicine*, 159(15):1681–89.

Rocha-Silva, L. (1992). *Alcohol, Tobacco and Other Drug Use: Young South Africans (10–24 years)*. Pretoria: HSRC.

Room, R., Jernigan, D., Carlini-Marlatt, B., Gureje, O., Mäkelä, K., Marshall, M., Medina-Mora, M.E., Monteiro, M., Parry, C., Partanen, J., Riley, L. & Saxena, S. (2002). *Alcohol in Developing Societies: A Public Health Approach*. Vol. 46. Helsinki: Finnish Foundation for Alcohol Studies, in collaboration with the World Health Organization.

Ryan, T. (1997). *Drugs, violence and governability in the future South Africa*. Occasional Paper No. 22 – May 1997. Available from: http://www.iss.co.za/pubs/papers/22/paper22.html; accessed 11 September 2007.

Saloojee Y. (2006). Tobacco control in South Africa. In K. Steyn, J. Fourie & N. Temple, (eds). *Chronic Diseases of Lifestyle in South Africa: 1995–2005*. Technical Report, South African Medical Research Council. Available from: http://www.mrc.ac.za/chronic/cdl 1995-2005.pdf; accessed 12 July 2011.

SAPA. (1995). New SA is narcotics ring's dream. *Evening Post*, 29 November.

Schneider, M., Norman, R., Parry, C., Bradshaw, D. & Plüddemann, A.; South African Comparative Risk Assessment Collaborating Group. (2007). Estimating the burden of disease attributable to alcohol use in South Africa in 2000. *South African Medical Journal*, 97:664–72.

Shisana, O., Peltzer, K., Zungu-Dirwayi, N. & Louw, J.(2005). *The Health of our Educators: A Focus on HIV/AIDS in South African Schools*. Cape Town: HSRC Press.

Shisana, O., Rehle, T., Simbayi, L.C., Parker, W., Zuma, K., Bhana, A., Connolly, C., Jooste, S. & Pillay, V. (eds). (2005). *South African National HIV Prevalence, HIV Incidence, Behaviour and Communication Survey 2005*. Cape Town: HSRC Press.

Shisana, O., Rehle, T., Simbayi, L.C., Zungu, N.P., Zuma, K., Ngogo, N., Jooste, S., Pillay-Van Wyk, V., Parker, W., Pezi, S., Davids, A., Nwanyanwu, O., Dinh, T.H. & SABSSM III

Implementation Team. (2009). *South African National HIV Prevalence, HIV Incidence, Behaviour and Communication Survey 2008*. Cape Town: HSRC Press.

Stein, D.J., Williams, D.R. & Kessler, R.C. (eds). (2009). The epidemiology of psychiatric disorders in South Africa: The SASH survey. *South African Medical Journal*, 99(5S2).

Steyn, K., Bradshaw, D., Norman, R., Saloojee, Y. & Laubscher, R. (2002). Tobacco use in South Africans during 1998: the first demographic and health survey 1998. *Journal of Cardiovascular Risk*, 9(3):161–70.

Steyn, C. (1996). 'Paradise' is closing down its borders. *The Star*, 13 March.

Swart, D., Reddy, P., Pitt, B. & Panday, S. (1999). The prevelance and determinants of tobacco-use among Grade 8–10 learners in South Africa. *The Global Youth Tobacco School-based Survey*. Pretoria: Medical Research Council.

Terblanche, S.S. & Venter, D. (1999). Drug abuse amongst high school pupils. *Social Work*, 22:161–78.

United Nations Office on Drugs and Crime (UNODC). (2002). *South Africa: Country Profile on Drugs and Crime*. Pretoria: UNODC.

United Nations Office on Drugs and Crime (UNODC). (2003). *Strategic Programme Framework on Crime and Drugs for Southern Africa*. Pretoria: UNODC.

United Nations Office on Drugs and Crime (UNODC). (2006). *World Drug Report*. Vienna: UNODC.

United States Department of State. (1996). *International Narcotics Control Strategy Report – South Africa*. Washington, DC: US Department of State.

Van Walbeek, C. (2002). Recent trends in smoking prevalence in South Africa – some evidence from AMPS data. *South African Medical Journal*, 92:468–72.

Visser, M. & Moleko, A. (1999). High-risk behavior of primary school learners. *Urban Health and Development Bulletin*, 2(1):69–77.

2 The clinical presentation of substance-related disorders in South Africa

Don Wilson, Henk Temmingh and Allanah Wilson

The substance-related disorders cover a wide variety of disorders, ranging from intoxication to dependence to psychosis – all as a result of using drugs of abuse or alcohol, or as the side effects of prescribed medication or the exposure to toxins.

Substances (drug of abuse, medication or toxin) can be divided, for convenience and because of similar clinical and pharmacological action, into three major classes: depressants (represented by alcohol, opiates and sedative/hypnotics and anxiolytics); stimulants (represented by cocaine, methamphetamine, amphetamine and similarly acting sympathomimetics); and hallucinogens (represented by LSD, PCP and mescaline). In this chapter we will also cover cannabis/marijuana. However, nicotine and inhalants (eg, glue, paint thinners and petrol) – intentionally inhaled volatile substances used to become intoxicated but frequently resulting in cognitive and mood disturbances – will not be discussed.

No class is absolute or agreed to by all, so cannabis, for example, could be placed among the hallucinogens or in a class of its own with hashish. Phencyclidine can be classified either with the hallucinogens or the stimulants, whereas methamphetamine can be classified with the stimulants or, in some classificatory systems, in the so-called designer-drug category.

South Africa follows worldwide trends in having alcohol as its major substance that is misused, with up to 6% of the population being classified as heavy drinkers (five or more drinks on the same day on at least five of the past 30 days), with quite large variations in sections of the population. Parry estimates that roughly one in four adult males and one in 10 adult females in South Africa experience symptoms of alcohol abuse (Parry, 2005). Alcohol is the most widely used psychoactive substance, followed by nicotine, with 43% of patients in specialist substance abuse treatment centres in South Africa reporting alcohol as the primary substance of abuse, and over half of patients having alcohol as a primary or secondary drug of abuse (SACENDU, 2006). However, it has been recognised that individuals with alcohol problems are very likely to be using other substances as well, and therefore polydrug or polysubstance abuse or dependence should be considered in all substance users.

Substance users present to clinics via various routes, with the most common of these being pressure by families and friends, because of work-related absenteeism, via legal and financial sources (for non-payment of bills and maintenance), by the medical route (accident emergency services or general practitioners) and as self-referrers. For medical practitioners, the taking of a substance-use history should be mandatory in all patient contacts.

In the DSM-IV-TR classification, the Substance-Related Disorders are divided into two groups: the Substance Use Disorders, namely, Abuse and Dependence; and the

Substance-Induced Disorders (American Psychiatric Association, 2005), under which the following will be discussed:

- Intoxication (with or without delirium)
- Withdrawal (with or without delirium)
- Dementia
- Amnestic disorder
- Psychotic disorders
- Mood disorders
- Anxiety disorders.

Substance abuse, dependence and addiction

Substance abuse (as it is referred to in the DSM-IV) or harmful use (as referred to in the ICD-10) consists of the presence of behaviour while under the influence of a substance that results in demonstrable adverse social, occupational, psychological, legal or physical consequences to the person involved (see Table 2.1 for ICD-10 Diagnostic Research Criteria). The ICD-10 differs from the DSM-IV in that abuse is termed 'harmful use' and the criteria are less specific than the DSM-IV-TR criteria. ICD-10 requires symptoms to be present for at least one month or repeatedly within a 12-month period. The DSM-IV-TR specifies four different criteria associated with persistent use of the substance. These criteria include:

- A failure to fulfil social and occupational role responsibilities
- Using substances in circumstances that are physically hazardous, such as driving under the influence
- Negative consequences in interpersonal relationships
- Frequently in trouble with the law as a result of substance use.

The DSM-IV requires at least one out of four criteria to be present during any period in 12 months and that symptoms should lead to significant impairment and distress (American Psychiatric Association, 2005; World Health Organization, 1992).

Substance dependence is a syndrome characterised by compulsive use of the substance and loss of control over substance-using behaviour. It can be accompanied by the phenomenon of tolerance to the effects of the substance and substance-specific withdrawal syndromes. Tolerance is characterised by the need for increased amounts of the substance to achieve the same desired effect, or by the same dose not resulting in the desired effects. Withdrawal is constituted by a characteristic cluster of symptoms on cessation or reduction of the substance. If either tolerance or withdrawal are present, ICD-10 and DSM-IV allow the subtype specification of physiological (DSM-IV) or physical dependence (ICD-10) to be noted. Substance-dependent individuals also spend increasing durations of time engaging in substance-taking behaviour and may give up other activities previously enjoyed in order to use the substance. Substance use continues compulsively despite adverse consequences to the person's psychological or physical health. Table 2.1 contains the ICD-10 criteria for harmful use and dependence.

The term 'addiction' is often used interchangeably with substance dependence. Addiction can be defined as a chronic relapsing medical disorder characterised by loss of control over substance intake, and compulsive drug use associated with the development of

Table 2.1: ICD-10 criteria for harmful use and dependence

Harmful use:
Mental or physical harm that may be associated with impaired judgment clearly caused by use of a substance within a 12-month period. ■ There must be clear evidence that the substance use was responsible for (or substantially contributed to) physical or psychological harm, including impaired judgment or dysfunctional behaviour. ■ The nature of the harm should be clearly identifiable (and specified). ■ The pattern of use has persisted for at least 1 month or has occurred repeatedly within a 12-month period. ■ The disorder does not meet criteria for any other mental or behavioural disorder related to the same drug in the same time period (except for acute intoxication).
Dependence syndrome:
Three or more of the following manifestations should have occurred together for at least one month or, if persisting for periods of less than one month, should have occurred repeatedly within a 12-month period: 1) A strong desire or sense of compulsion to take the substance 2) Impaired capacity to control substance-taking behaviour in terms of its onset, termination or levels of use, as evidenced by the substance being often taken in larger amounts over a longer period than intended, or by a persistent desire or unsuccessful efforts to reduce or control substance use 3) A physiological withdrawal state when substance use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome for the substance or by use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms 4) Evidence of tolerance to the effects of the substance, such as that there is a need for significantly increased amounts of the substance to achieve intoxication or the desired effect, or a markedly diminished effect with continued use of the same amount of the substance 5) Preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use; or a great deal of time spent in activities necessary to obtain, take or recover from the effects of the substance 6) Persistent use of substance despite clear evidence of harmful consequences, as evidenced by continued use when the individual is actually aware, or may be expected to be aware, of the nature and extent of harm.

Source: World Health Organization, 1992

neuro-adaptations that result in the presence of negative affective states when the substance is withdrawn (Koob, 2009).

Instruments used in screening and diagnosis

Several screening tools exist to aid the identification of early-stage, problem alcohol and drug use. The primary aim of most screening instruments is not to establish a diagnosis but merely to identify problem drug-use behaviours, which may include clinically relevant

disorders or merely at-risk behaviours that have the potential of developing into clinical disorders. Within the clinical context, time constraints often limit the use of some of these tools, and consequently not all of them are suitable for routine clinical use. The Alcohol Use Disorders Identification Test, or AUDIT (Saunders et al, 1993), is a brief (two-to-three-minute) 10-item screening tool of particular use in primary care, general practice settings (see Table 2.2). It includes both a self-report and clinician-administered version that rate items relating to different aspects of drinking patterns, harmful use and dependency on a four-point Likert-type scale ('never' to 'daily' or 'almost daily'). A total score of more than 8 on this scale is indicative of alcohol-related problems that call for further in-depth diagnostic interviewing. Lower cut-off scores than 8 are suggested for female populations. This instrument has demonstrated good sensitivities, varying from 0.76 to 0.92 and specificities from 0.70 to 0.92 in various populations, including psychiatric patients with severe mental illness and primary care patients (Reinert & Allen, 2002). This instrument has also been translated into Xhosa (Smit et al, 2006).

The Drug Use Disorders Identification Test, or DUDIT, is a similarly useful 10-item screening tool derived from the AUDIT to screen for substance (other than alcohol) abuse and dependence (Berman et al, 2005).

The Michigan Alcoholism Screening Test, or MAST (Selzer, 1971), is a slightly more comprehensive instrument that, in addition to current alcohol use, also assesses use over the subject's entire lifetime. This self-report screening instrument consists of 25 yes or no items and is available in two shorter 13- and 10-item versions. It is suitable for a variety of clinical and non-clinical settings. In addition to assessing alcohol use, it also enquires about a number of related consequences of alcohol abuse, such as medical, psychological, psychiatric, social, interpersonal and occupational complications. Despite its strength as regards comprehensiveness, it is less likely to be suitable in busy, time-pressured clinical settings.

The Drug Abuse Screening Test, or DAST (Skinner, 1982), is a self-report instrument based on the MAST but specific to illicit drug use. Similar to the MAST, it assesses the presence of a variety of social, occupational, interpersonal and medical consequences relating to illicit non-medical drug use.

A brief and clinically useful tool to identify alcohol-related disorders is the CAGE questionnaire (Ewing, 1984). This instrument is widely used in clinical settings in the South African context. This very brief instrument takes less than one minute to complete and consists of four brief questions as contained in the acronym 'CAGE':

- **C**ut down – refers to the need to cut down or decrease drinking
- **A**nnoyed – refers to feeling annoyed at criticism from others about drinking too much
- **G**uilt – refers to feeling bad or guilty about drinking
- **E**ye-opener – refers to the need to have a drink first thing in the morning.

The total score of the test is out of 4. A cut-off of 1 out of 4 has a high sensitivity, varying from 0.86 to 0.90, but lower specificity (and hence a higher false positive rate), ranging from as low as 0.52 to 0.53, to detect alcohol-use disorders of clinical threshold (abuse and dependence as identified by DSM or ICD-10 criteria). Consequently, some have recommended that a cut-off of ≥2 be used to identify abuse or dependence, as a result of the higher specificity and hence lower false positive rate of higher cut-offs. Clinicians also need to be aware of its

Table 2.2: Alcohol Use Disorders Identification Test (AUDIT)

Please circle the answer that is correct for you	
1. How often do you have a drink containing alcohol? (0) Never (1) Monthly or less (2) 4 times a month (3) 2–3 times a week (4) 4 or more times a week	6. During the past year, how often have you needed a drink in the morning to get yourself going after a heavy drinking session? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
2. How many standard drinks containing alcohol do you have on a standard day when drinking? (0) 1 or 2 (1) 3 or 4 (2) 5 or 6 (3) 7 to 9 (4) 10 or more	7. During the past year, how often have you had a feeling of guilt or remorse after drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
3. How often do you have six or more drinks on one occasion? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily	8. During the past year, have you been unable to remember what happened the night before because you had been drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
4. During the past year, how often have you found that you were not able to stop drinking once you had started? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily	9. Have you or someone else been injured as a result of your drinking? (0) No (2) Yes, but not in past year (4) Yes, during the past year
5. During the past year, how often have you failed to do what was normally expected of you because of drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily	10. Has a relative or friend, doctor or other health care worker been concerned about your drinking and suggested you cut down? (0) No (2) Yes, but not in past year (4) Yes, during the past year

Note: A total score of 8 or more is associated with harmful or hazardous drinking, and a score of 13 or more in women, and 15 or more in men, is likely to indicate dependence.
Source: Saunders, Aasland, Babor et al, 1993

limitations in certain populations, as studies have shown it to be a less accurate instrument in white women, pregnant women and college students who tend to binge drink (Dhalla & Kopec, 2007).

In addition to non-structured clinical diagnostic classification systems, such as the ICD-10 and DSM-IV, more structured instruments exist to aid in the diagnosis of substance abuse and dependence. The Structured Clinical Interview for DSM-IV, or SCID-I (First et al, 1994), is a semi-structured clinical interview designed to generate categorical diagnoses based on DSM-IV diagnostic criteria. To conduct this interview successfully, formal training is required; experience and background in clinical work is advantageous, although not essential.

The Mini International Neuropsychiatric Interview, or MINI (Sheehan et al, 1998) is a briefer diagnostic instrument in comparison to the SCID-I, and one that generates a wide variety of diagnoses, including substance- and alcohol-use disorder categories. The MINI is available in a variety of languages, including English and Afrikaans, and takes approximately 15–20 minutes to complete.

The MINI questions are structured to be delivered verbatim and have a yes/no outcome. This instrument has been designed to maximise sensitivity, introducing the possibility of false positives and therefore necessitating more in-depth probing by clinicians in cases where positive predictive values need to be maximised (the likelihood that a positive screen represents a true positive).

The most widely used scale in the measurement of addiction severity within addiction treatment settings is the Addiction Severity Index, or ASI (McLellan et al, 1992). This multidimensional instrument measures the consequences of drug use across seven domains, including the assessment of drug and alcohol use, medical consequences, psychiatric complications, impacts on employment and support, family history, family and social support and legal status. This scale requires training to administer, and takes 40–60 minutes to complete. Severity can be calculated by calculating composite scores or by means of a clinician-rated severity scale for each measured domain. It can be used to track treatment progress over time. Its limitations include low test/retest reliability in some populations, such as in dual-disorder, severely mentally ill and homeless individuals, and lower inter-rater reliabilities among interviewers with less training. The calculation of composite scores, as opposed to clinician-rated severity scales, has been recommended in follow-up studies (McLellan et al, 2008; Mäkelä, 2004).

Differentiation of primary versus secondary mental disorders

In the South African context, high rates of co-occurring substance use disorders characterise populations with severe mental illness, with prevalence rates often in excess of 50% (Weich & Pienaar, 2009). When comorbidity is present, this is likely to require integrated treatment approaches in order to achieve improved outcomes (Horsfall et al, 2009). In addition, comorbidity introduces the problem of differentiating substance-induced syndromes from primary mental disorders.

Depending on the background and needs of healthcare professionals involved in the treatment of mental disorders that co-occur with substance use disorders, various standpoints can be delineated in relation to the importance of questions relating to diagnosis

and aetiology. Thus clinicians, scientific researchers, treatment researchers, epidemiologists, medical insurance companies and policy-makers have differing needs in relation to diagnostic classification systems such as the DSM-IV and ICD-10 (Hasin et al, 2007). Despite differing views, needs and emphasis, common to all is the need to determine the bio-psychosocial determinants that aid the successful integrative treatments of mental disorders that co-occur with substance use.

Guidelines derived from the DSM-IV and related structured clinical instruments, such as the SCID-I, contain several pointers to aid in the differentiation of primary versus substance-induced disorders. These guidelines rest on principles of causality, such as the specificity of the causative drug in causing particular syndromes, biological plausibility, discontinuation of symptoms on the removal of exposure and, perhaps most importantly, issues relating to the temporality of exposure and disease outcome. One pertinent criticism of the DSM-IV is that assumptions are made about causality despite its intention to describe disorders from an atheoretical point of view (Nunes & Rounsaville, 2007). Thus very few studies have clearly demonstrated, for example, that substance-induced psychosis is caused by any particular drug, although the DSM-IV makes the assumption that substance-induced psychosis is indeed 'induced' or caused by a particular substance. This is opposed to the notion that drugs which 'induce' disorders may in fact just represent a component risk factor within complex sufficient-causality models for psychosis or indeed schizophrenia itself. Therefore it has been suggested that a more neutral position needs to be adopted regarding causality with less reliance on inductive reasoning for future classification systems, including the DSM-5. Nevertheless, it is important for longer-term treatment planning to obtain a degree of diagnostic certainty to minimise over- or under-exposure to psychotropic drugs treating mental disorders.

The Psychiatric Research Instrument for the Substance and Mental disorders, or PRISM (Caton et al, 2005; Hasin et al, 1996), is a tool that has been designed specifically to differentiate between primary and substance-induced mental disorders. This instrument contains more explicit and rigorous operationalised diagnostic rules and definitions describing substance-induced disorders and primary mental disorders. In addition, it stipulates more specific and explicit rules regarding the temporal relationships between the onset of mental symptoms and the onset of substance use and substance use disorders. After data collection, diagnoses can also be generated using computer algorithm programs to minimise bias. One study in a Spanish population, utilising longitudinal observation, expert diagnosis and all available data or LEAD criteria as the gold standard, has demonstrated that diagnoses generated by the PRISM are more reliable and valid than SCID-generated diagnoses (Torrens et al, 2004).

Within the clinical setting, it is advisable to conduct repeated clinical assessments over time in order to establish an accurate diagnosis. This is particularly the case in the acute inpatient setting where the co-occurrence of significant substance use and severe mental symptoms can often lead to lack of clarity on diagnosis due to a variety of reasons. The initial diagnosis of a patient presenting with a significant substance-related disorder should be conservative, and over-diagnosis of a primary mental disorder should be avoided. At the same time, clinicians must use their clinical judgment as to the need for medications such as antipsychotics and antidepressants, and under-treatment should also be avoided. Treatment with antipsychotics may, however, need to be tapered sooner in cases where clinicians gain more certainty that a mental disorder was indeed substance-induced. In many cases,

the final diagnosis can only be made after several months of assessment, which includes a detailed assessment of chronology of symptoms, persistence of symptoms during periods of abstinence, various risk factors such as family history and changes in social and occupational functioning (Ross, 2008). Longitudinal Expert and All Data (LEAD) criteria should be the rule rather than the exception in setting a gold standard to determine diagnosis in mental disorders associated with substance use. Table 2.3 contains some diagnostic guidelines to aid in the distinction of primary versus substance-induced mental disorders as well as the problems, caveats and controversies surrounding some of these principles.

Table 2.3: Diagnostic guidelines and controversies in the differentiation of primary versus substance-related disorders

PRIMARY VERSUS SUBSTANCE-INDUCED MENTAL DISORDERS	
Diagnostic guidelines	Problems, caveats and controversies
1. Primary disorders have their onset prior to significant substance use, abuse and dependence	1. Primary disorder can still develop on a baseline of chronic steady use
2. Substance-induced disorders should include symptoms that are in excess of what would be expected from intoxication or withdrawal.ICD-10 but not DSM-IV requires psychotic symptoms to meet full base disorder criteria (for schizophrenia or major depression)	2. What constitutes symptoms in excess? Are full syndromal criteria necessary for substance-induced disorders, or can sub-syndromal symptoms suffice (DSM-IV, i.e. depression without full MDE criteria; delusions in the absence of hallucinations or thought disorder)?
3. 'Substance-induced' refers to a state of disorder that is beyond that expected from intoxication or withdrawal	3. Assumptions of causality (disorders are induced by substances) in absence of clear empirical evidence base. Suggestion to term conditions 'substance-related' or '-associated' rather than 'induced'
4. Substance-induced psychosis in ICD-10: symptoms continue beyond 48 hours of last use, have onset within two weeks of use and not continue longer than six months	4. Protracted withdrawal syndromes can be present in certain substances with longer half-life beyond 48 hours or even longer than one month
5. DSM-IV. Symptoms that persist beyond about one month (to six weeks) of abstinence should be considered primary	5. ICD-10 symptoms can be present for up to six months after start of abstinence and can still be considered 'substance-induced'
6. Primary disorder needs to be considered if there is evidence from the history of an independent non-substance-related mental disorder, such as a recurrent mental disorder occurring during periods of minimal drug use or long periods of abstinence	6. Problems in retrospective assessment due to quality of information, recall limitations or bias, limits this as a measure of an independent mental disorder

Sources: Mathias et al, 2008; Saunders et al, 2007

Towards the DSM-5

At the time of writing, the DSM-5 task force and working group have made some suggestions as to the possible format of the DSM-5. This includes the reintroduction of the term 'addiction' to distinguish benign states of dependence on medications such as, for example, SSRI and beta blockers and associated withdrawal syndromes, in comparison to functionally impairing and dysfunctional dependency syndromes characteristic of drug addiction. The committee has made a recommendation that the DSM-5 should not contain the separate condition of abuse or dependence but that these be collapsed into a single disorder category named 'substance use disorders' containing 11 operationalised criteria. These criteria will essentially be a collapse of the existing DSM-IV abuse and dependence criteria. The proposed new criteria set excludes the requirement for recurrent substance-related legal problems and includes an item formerly not part of the DSM-IV but part of the ICD-10 relating to craving for substances. The counting of criteria has been suggested to determine a threshold diagnosis which is then used to generate a moderately severe disorder category in the case of 2–3 out of 11 symptoms, and a severe category of 4 or more out of 11 symptoms. Furthermore, an additional category for cannabis withdrawal will be considered for the DSM-5 following increasing epidemiological, clinical and neuroscientific evidence of the presence of such a syndrome (Kupfer & Regier, 2010).

The substance-induced disorders

The substance-induced disorders are covered here in broad strokes, with more specific details regarding clinical presentation of particular substances presented later.

Delirium (due to intoxication or withdrawal)

- Dementia
- Amnestic disorder
- Psychotic disorders
- Mood disorders
- Anxiety disorders

In these disorders, there should be evidence from history, collateral, physical examination or special investigations to show that specific substance/s were directly implicated aetiologically in the disorder (see Table 2.3). Intoxication or withdrawal can temporarily mimic some of these major psychiatric disorders, and so it is probably wise to delay making these diagnoses immediately.

Substance-induced delirium

This delirium is due to an intoxication (use of the substance in larger quantities or over longer periods) or due to withdrawal of the substance. This disorder develops over a short time and fluctuates over the course of the day.

The major features that are present include:

- Disturbance in the level of consciousness developing rapidly over hours or days, with a fluctuation and variability of severity over the course of the day.

- Difficulty in focusing attention and in sustaining or shifting attention, and the individual is easily distracted. This can lead to difficulty in taking a history.
- Cognitive changes, which involve poor recent memory, disorientation (mainly for time and place) and poor social judgment.
- Speech and language and thought disturbances can manifest as rambling, to pressured and incoherent communication. The individual may become suspicious to frankly delusional.
- Perceptual disturbances, with misinterpretations of the environment with illusions and hallucinations (commonly auditory and visual, but also olfactory and tactile).
- Some associated features may be disturbance in the sleep-wake cycle, with agitation and restlessness mainly at night and daytime drowsiness. There can also be changes in psychomotor activity – frequently with increased activity to sluggishness or apathy. When the patient is overactive there is a concurrent increase in all the major manifestations.
- Emotional or affective variability or instability, with the patient shifting through a variety of emotional states, from anxiety, anger, depression and irritability to euphoria and apathy.

Substance-induced (persistent) dementia

This dementia is described as persisting because it continues long after the patient has experienced the effects of an intoxication or withdrawal, and in some instances even after intake of the substance has been stopped (eg, alcohol). It usually has an insidious and slow progression, and usually manifests later in life. In many instances it is permanent, although in some substances there can be improvement (eg, benzodiazepines). This dementia can occur in association with the following substances: alcohol, inhalants, sedatives/hypnotics/anxiolytics, and industrial solvents.

The disorder presents with multiple cognitive deficits, which include poor memory (typically, recent memory, and involving some difficulty recalling past events) and disturbances of executive functioning (planning and decision-making, organising, sequencing and abstractive thinking), as well as varying degrees of severity in one or more of the following: aphasia (speech becomes vague and empty); apraxia (difficulty in executing known motor activity, manifesting in difficulty dressing, tying shoelaces and other everyday routine motor activities); or agnosia (inability to recognise common objects). The severity is such that it causes impairment in personal, social or occupational functioning, and is usually noted by others as a decline in functioning.

As the disease progresses, there are disturbances in behaviour: sleep patterns are disturbed, and patients become lost, act aggressively, become emotionally labile, have impaired personal hygiene and injure themselves falling because of poor motor coordination. Patients can become deluded and hallucinated and accuse caregivers and family irrationally. Because of their frail health, they are liable to infections, and superimposed delirium is common.

Substance-induced amnestic disorders

These disorders are marked by an inability to learn new information and/or an inability to recall recent information or, in some individuals, past events. The extent of the deficit depends on the severity of brain damage. This diagnosis should not be made if

the individual is either in a delirium or demented. This deficit is best observed when requesting spontaneous recall of recent information. There is sometimes confabulation where memory gaps are filled by imaginary events, but this tends to diminish over time (here the importance of collateral is important). Individuals with amnesia are frequently unaware of their deficits and deny memory impairment, and if aware of some change appear unconcerned when confronted. Associated with this deficit can be a lack of drive and initiative and a suggestion of more subtle cognitive changes which are not sufficient to make a diagnosis of dementia.

The classic amnestic disorder is Korsakoff's psychosis (see under alcohol-induced disorders).

Substance-induced psychotic disorders

These are diagnosed if there are prominent hallucinations and delusions, and should only occur in association with substance-induced intoxication or withdrawal states that are in excess of what one would expect and which would require attention in their own right. Once initiated, they can persist for weeks, but more commonly persist as long as substance use continues. By definition, this psychosis should settle once the effects of the substance have been withdrawn. However, with some substances, particularly methamphetamine, the psychotic features persist well beyond what the pharmacokinetics of the drug would suggest.

Alcohol-induced hallucinations are usually auditory and frequently persecutory in nature. Stimulants produce persecutory hallucinations, as well as tactile or somatic hallucinations of insects or bugs under the skin (formication), which can lead to scratching and skin excoriation, as well as perceptual distortions and misperceptions of the environment. Cannabis can also produce persecutory hallucinations and time distortion, as well as extreme anxiety and emotional lability.

The substance-induced psychoses should be differentiated from primary psychotic disorders (sometimes with immense difficulty) by taking into account the basics, namely, history, physical examination and special investigations demonstrating dependence or abuse, and then looking for features such as abrupt onset, a course which demonstrates a reduction of symptoms once the substance is stopped, atypical age of onset and other unusual factors – for example, prominent visual hallucinations, formication and major behavioural disturbances, disinhibition and aggression (see Table 2.3).

One must always consider that the presenting psychosis could be a primary psychosis precipitated by the use of substance. In South Africa there is associated substance use in many of our admissions to state hospitals, so substances are frequently a confounding factor in making a diagnosis.

Psychotic disorders can be associated with intoxication with the following substances: alcohol, amphetamines/cocaine and other stimulants, cannabis, hallucinogens (phencyclidine), inhalants, opioids and sedative/hypnotic/anxiolytics. Similarly they can occur on withdrawal from alcohol and sedative/hypnotic/anxiolytics.

Substance-induced mood and anxiety disorders

Substance-use disorders and mood and anxiety disorders are widespread among the general population, and have strong associations when considered on a lifetime basis. However, the

prevalence of substance-induced mood and anxiety disorders among a sample representing 19.3 million US respondents with any current mood and anxiety disorders was less than 1% (Grant et al, 2004).

Substance-induced mood and anxiety disorders are diagnosed if there are prominent and persistent disturbances of mood that are seen to be due to the direct effects of a substance. These mood disturbances can be either a depressed mood or diminished interest or pleasure, or hypomanic/manic response with elevated, expansive or irritable mood or mixed states, but do not have to meet the full DSM-IV criteria for these episodes for the diagnosis to be made. However, to be given a specific diagnosis and clinical attention, these mood disturbances should be in excess of what one would expect in an intoxicated or withdrawal state, they should occur during a period of substance use and they should not persist for more than four weeks after cessation of the substance.

Clinical features of specific substances

Depressants

Alcohol-induced disorders

The clinical consequences of an overuse of alcohol can be **intoxication**. This usually involves some disinhibition, with excitement and elevated mood, followed by drowsiness, sleepiness, irritability or depression. If, however, excessive quantities are consumed, the final outcome can be coma and even death (from respiratory depression or aspiration of vomit). All of the above are influenced by the quantity consumed, speed of drinking, percentage of alcohol per drink and whether or not the individual has eaten. In regular heavy drinkers, the effect may be less because of the tolerance, where alcohol metabolism is increased and the person also has learned to cope with larger quantities of alcohol and may appear sober despite high blood alcohol levels.

Blackouts (brief amnestic periods or events) are common among heavy drinkers and are often described as the 'lost evening' or 'lost weekend'. It is suggested that this memory is state-bound, and when these individuals are next intoxicated they will be able to access these memories.

If an acutely intoxicated patient does arrive in a clinical setting, he or she requires reassurance and maintenance in a safe and monitored environment, with efforts to decrease external stimulation and provide orientation and reality testing. Adequate hydration and nutrition should be provided. Clinical assessment should be performed, with an emphasis on general medical and mental status, substance use history and any associated social problems. Patients presenting with signs of intoxication should also be assessed for the possibility of recent use of other substances that could complicate the clinical course. Patients with a history of prolonged or heavy drinking or a past history of withdrawal symptoms are at particular risk for medically complicated withdrawal syndromes, which may require hospitalisation.

Withdrawal

One of the core features defining alcoholism is withdrawal, which starts within 8 to 10 hours following the last drink and reaches its maximum within 24 to 48 hours. It can be defined on a continuum from mild to moderate to severe.

The syndrome of mild to moderate alcohol withdrawal generally occurs within the first 8–12 hours after cessation or reduction of heavy, prolonged ingestion of alcohol. It includes such signs and symptoms as gastrointestinal distress, tremulousness, anxiety, irritability, elevated blood pressure, tachycardia and sweatiness.

The syndrome of severe alcohol withdrawal (or delirium tremens) occurs within 24 to 72 hours after cessation or reduction of heavy, prolonged ingestion of alcohol, and can last in some individuals up to 14 days. The syndrome includes the above signs and symptoms as well as clouding of consciousness, difficulty in sustaining attention, disorientation, grand mal seizures, hallucinations, behavioural disturbances, alcohol craving and fever.

This is a medical emergency, and all patients with severe alcohol withdrawal/delirium tremens should be admitted and managed and monitored carefully. Fewer than 5% of individuals with alcohol withdrawal develop severe symptoms, and fewer than 3% develop grand mal seizures (Institute of Medicine, 1990).

Those at risk for delirium tremens include those with previous history of delirium tremens, the elderly, those with poor nutrition and those with pre-existing brain injury.

Alcoholic withdrawal hallucinations usually occur in association with delirium tremens, but can occur without other signs of withdrawal. These usually begin within 48 hours of stopping or reducing alcohol. The duration can be brief (from a few minutes to days). In some instances, hallucinations may remain as a chronic disorder (alcoholic hallucinosis). The hallucinations are mainly visual, auditory or mixed.

Alcohol-induced dementia is usually secondary to prolonged and persistent alcohol use in those with poor nutrition and consequent vitamin deficiency, particularly thiamine (vitamin B1). This dementia is often preceded by an untreated amnestic disorder originally described as Korsakoff's psychosis, which entailed amnesia, characterised by anterograde and retrograde amnesia, disorientation, poor recall and impairment of recent memory, coupled with confabulation and ataxia. In more than half of the patients, elements of Korsakoff's syndrome are permanent (Xiong & Daubert, 2009).

Alcohol-induced mood and anxiety disorders

Up to 80% of alcoholics complain of depressive symptoms at some time in their lives, and up to 30% have features which fulfil the criteria for a major depressive episode (Kessler et al, 1997). Are these substance-induced mood disorders (alcohol is a depressant drug and intoxication can be accompanied by short-term, sometimes severe depressive symptoms which can last up to 2–4 weeks after active drinking has ceased), or do they reflect an underlying medical problem (eg, liver or pancreatic disorder or the consequence of medication), or are they related to independent major depressive episodes? The symptoms are phenomenologically similar no matter what the cause. The importance of this relates to the correct future management of this mood disorder (Raimo & Schuckit, 1998).

Features of alcohol-induced mood disorders are as follows:

- The rates of depression are high during intoxication in alcohol-dependent individuals, and resolve over a few weeks to a month in the majority of depressed alcoholics on abstinence. Perhaps deferring antidepressant treatment for at least four weeks after discontinuing drinking should be the recommended treatment.

- They do not have an increased family history of major depressive disorder, and major depressive disorders are not observed in higher rates in children of alcoholics.
- Based on timeline interviews with alcoholics, prospective studies do not show much higher rates of independent major depressive disorders as compared to controls (Raimo & Schuckit, 1998).

Alcohol-induced medical disorders

Prospective studies show that alcoholics have higher rates of mortality and medical morbidity than matched controls (Klatsky et al, 1992). The most common causes of early death among people with alcoholic dependence are heart diseases. Although one to two drinks daily are cardio-protective, larger quantities are damaging, resulting in hypertension, increased triglycerides and low-density lipoprotein cholesterol and risk for deterioration of heart muscle, cardiomyopathy and ischaemic heart disease. After heart diseases comes cancer, related to the effects of heavy alcohol use on the immune system, and which leads to malignancies especially to the head and neck, oesophagus and stomach and also to the respiratory tract (most alcoholics are smokers). Cancer as a cause of death is followed by accidents and suicide. The many other medical consequences of substance dependence are as follows:

- **Chronic high-dose alcohol use** can affect several different organ systems, including the gastrointestinal tract, the cardiovascular system and the central and peripheral nervous systems. Alcohol-induced gastrointestinal problems include gastritis, ulcers of the stomach or duodenum, and, in approximately 15% of heavy users, cirrhosis of the liver and pancreatitis.
- **Endocrine consequences** of chronic alcohol use for men include decreases in serum testosterone, loss of facial hair, breast enlargement, decreased libido and impotence. Consequences for women include amenorrhoea, luteal phase dysfunction, anovulation, early menopause and hyperprolactinaemia.
- **Alcohol-induced peripheral myopathy** with muscle weakness, atrophy, tenderness, and pain is accompanied by elevations in creatine phosphokinase levels and the presence of myoglobin in the urine. Severe cases can involve rapidly progressive muscle wasting.
- **Nervous system sequelae** of chronic alcohol use are related to vitamin deficiencies, particularly deficiencies in thiamine and other B vitamins. They include peripheral neuropathies, cognitive deficits, severe memory impairment and degenerative changes in the cerebellum.
- **Cognitive abnormalities.** In long-standing alcoholics, dementia with characteristic cognitive deficits can occur (as discussed above). However, one more commonly sees a subtle cognitive dysfunction that still may hamper a patient's ability to comprehend or comply with a treatment plan. For such patients, active involvement of family members or other responsible parties should take place at the beginning of, and throughout, treatment. Initial placement in a more structured treatment setting may also be indicated to assess the impact of cognitive problems on the patient's ability to comply with short- and long-term treatment. In patients who remain abstinent, reversal of alcohol-induced cognitive disturbance is often observed over time.

- **Wernicke's encephalopathy,** which is characterised by ophthalmoplegia, ataxia and confusion. Ocular abnormalities include nystagmus, eye muscle palsies and pupillary abnormalities. The mortality rate for acute untreated Wernicke's encephalopathy is 15–20%. Recovery is incomplete in 40% of the cases.
- **Ataxia,** which is most often due to cerebellar dysfunction.
- Alcohol-related disorders may have adverse effects on the health of the pregnant woman, the course of the pregnancy, fetal development, early child development and parenting behaviour. The most well-established effect of *in utero* substance exposure is fetal alcohol syndrome. Reported effects of fetal alcohol syndrome in children exposed to high doses of alcohol *in utero* include low birth weight, poor coordination, hypotonia, neonatal irritability, retarded growth and development, craniofacial abnormalities (including microcephaly), cardiovascular deficits, mild to moderate retardation, childhood hyperactivity and impaired school performance.

Opioids

Opioid is the term used to describe the family of compounds related to opium. Opium is produced from the opium poppy *Papaver somniferum*. Morphine and codeine are examples of naturally occurring opioid alkaloids. Diacetylmorphine (heroin) is a semi-synthetic opioid, synthesised from morphine, whereas methadone, pethidine and dipipanone are examples of synthetic opioids (Ghodse, 2002).

Intoxication

Opioids bind to three main receptors in the central nervous system: mu (μ), delta (δ) and kappa (κ). Stimulation of all three receptors is thought to have an analgesic effect – hence the use of opioids as analgesics. Stimulation of the mu (μ) receptor is associated with euphoria and profound relief of anxiety; physical symptoms include cough suppression and the risk of respiratory depression, miosis (papillary constriction) and constipation. In contrast, stimulation of kappa (κ) receptors is often associated with sedation and dysphoria (Rastegar & Fingerhood, 2005; Stahl, 2008). There may also be cognitive impairment such as impaired attention, concentration and memory.

Heroin is preferred to morphine as a drug of abuse, as it has a more rapid and greater analgesic and euphoric effect and is less likely to cause unpleasant side effects such as nausea or constipation (Ghodse, 2000).

Tolerance develops to many, but not all, of the effects of opioids, so that increasing doses have to be taken to obtain the desired effect of analgesia or euphoria. However, tolerance does not usually develop to miosis and constipating effects.

Large doses of opioids may result in an overdose, and the risk of overdose is increased with the concurrent use of other CNS depressants such as alcohol and benzodiazepines. Opioid overdose can be recognised by depressed level of consciousness, decreased respiration (<8 breaths per minute) and pin-point pupils.

Withdrawal

Heroin is an opioid with a short duration of action, and so symptoms of withdrawal have an earlier onset, shorter duration and greater intensity than a longer-acting drug such as

methadone. Withdrawal typically occurs within 12 hours of discontinuation of regular use (Rastegar & Fingerhood, 2005). Depending on the opioid used, the duration of use and the quantity of opioid consumed daily, as well as personal factors such as the individual's own expectation of the withdrawal, the intensity of withdrawal response can vary from mild to moderate to severe. These withdrawal symptoms usually appear in the following order: anxiety, irritability and craving 8–12 hours after last dose, then dysphoria, lacrimation, rhinorrhoea, perspiration, restlessness, yawning and interrupted sleep. This is followed by piloerection (goose bumps – 'cold turkey'), hot and cold flashes or sweats, hypertension and tachycardia and a low-grade fever and mydriasis (dilated pupils), with the addition of either arthralgias and/or myalgias and muscle spasms and myoclonus, gastrointestinal distress, including nausea, vomiting and diarrhoea in more severe reactions, and consequent weight loss (Wilson & De Miranda, 2001).

Untreated heroin withdrawal symptoms typically reach their peak 32–72 hours after the last dose. Withdrawal symptoms generally resolve within a week of abstinence, but may be prolonged (Taylor et al, 2007). Once the acute symptoms have subsided, changes in the sleep pattern and dysphoric mood can persist for several months. These symptoms can all be modified by active treatment, discussed in Chapter 18.

Methaqualone

A combination of methaqualone and diphenhydramine, sold as Mandrax in South Africa, was initially marketed as a safer, less addictive sedative-hypnotic than the barbiturates, until evidence showed this to be false and that it was indeed highly addictive. It was subsequently banned (Weich, 2007).

In South Africa, illegally manufactured or imported methaqualone is available in tablet form, which is then crushed and sprinkled on cannabis and smoked in a pipe. During the 1980s and 1990s, methaqualone was the most commonly used illicit substance in South Africa. It has been since superseded by methamphetamine.

Intoxication

Methaqualone results in a feeling of intense euphoria and relaxation. Disinhibition is common, and there is a sense of heightened perception. The individual may experience impaired motor coordination and slurred speech, dizziness and syncope, hypersomnia, nausea and vomiting. The effects of methaqualone last for several hours (Wilson & De Miranda, 2001).

Withdrawal

Withdrawal symptoms start 12–24 hours after the individual's last dose, with symptoms peaking between day two and three. With withdrawal comes irritability and aggression. Physically, there is weakness, loss of appetite, nausea and vomiting, abdominal cramps, restlessness, tremor, headaches and insomnia. Many individuals experience brief withdrawal deliriums, and some may experience psychotic symptoms of hallucinations and delusions with hypomania that can last for two to three weeks (Wilson & De Miranda, 2001). This quite marked withdrawal response may be due to the fact that in South Africa methaqualone is used in conjunction with cannabis, and so one is getting a dual withdrawal.

The stimulants

Amphetamines and methamphetamine

Amphetamines are synthetic drugs, structurally related to ephedrine, which is an endogenous stimulant. When a methyl group is added to amphetamine, methamphetamine is formed, which crosses the blood-brain barrier more rapidly and results in methamphetamine's onset of action being faster. The stimulant effect of methamphetamine is similar to cocaine but has a much longer duration of action. Methamphetamine can be used in a powder or crystal form and is commonly smoked but can also be ingested, snorted or injected. In South Africa it is called tik, and is generally smoked.

Intoxication

Amphetamines, especially methamphetamine, cause the release of large quantities of neurotransmitters, such as dopamine, norepinephrine, epinephrine and serotonin. However its action on norepinephrine and serotonin is weaker than on dopamine receptors (Stahl, 2008). Methamphetamines result in the release of monoamines via multiple molecular processes, unlike cocaine, which principally disrupts the reuptake of dopamine from synapses (Barr et al, 2006).

Intoxication is associated with a 'high' or rush of intense euphoria, usually occurring within seconds, and feelings of increased wellbeing, energy, alertness and concentration that can last for 8–12 hours (Weich, 2007). Other psychological effects include increased libido and self-confidence, while undesirable effects such as agitation, irritability and aggression may occur. Because amphetamines are sympathomimetic drugs, they result in tachycardia, palpitations, hypertension and mydriosis. Other physical symptoms are dry mouth, hyperthermia, appetite suppression and insomnia (Rastegar & Fingerhood, 2005b).

A study monitoring methamphetamine-related presentations at psychiatric hospitals in Cape Town, done in 2009, showed the most common presenting symptom was aggressive behaviour (74%), followed by delusions (59%) and hallucinations (57%). Other symptoms were paranoid thoughts (52%), sleep disturbances (40%), thought disorders (39%), euphoric/elevated mood (27%), depressed mood (15%) and anxiety (10%). The most common combination of symptoms was aggressive behaviour/paranoid thoughts/delusions (30%) (Plüddemann et al, 2009).

Withdrawal

With withdrawal comes exhaustion, hyperphagia, depressed mood and severe craving. These features of withdrawal are similar to cocaine but, due to amphetamines' longer half-life, they may be delayed in onset and longer lasting (Rastegar & Fingerhood, 2005b).

Methamphetamine-induced psychosis

Methamphetamine psychosis may be sudden and short-lived, but in some individuals there may be enduring symptoms (Barr et al, 2006). Stimulant-induced psychotic symptoms were reported more frequently in methamphetamine users than in individuals who used cocaine (Mahoney et al, 2008). Individuals can be sexually disinhibited, aggressive and grandiose, with disorganised speech and ideas.

In the long term, methamphetamine acts as a neurotoxin shown to cause dopaminergic degeneration. Long-term use has been shown to cause neuropsychological deficits, especially deficits in attention, working memory and executive function (Barr et al, 2006). In non-human primates, dopamine functioning recovers over time (Melega et al, 1997).

Cocaine

Cocaine is an alkaloid prepared from the leaves of the coca bush, *Erythroxylum coca*. Cocaine is a powerful, short-acting central nervous stimulant. Cocaine is available in a powder form as cocaine hydrochloride, which can be 'snorted' or injected intravenously. Cocaine hydrochloride is unsuitable for smoking as it decomposes at high temperatures. 'Crack cocaine' is the term used for cocaine hydrochloride that has been processed to a free base by adding an alkali. It has a lower melting point, which makes it more conducive for smoking (Rastegar & Fingerhood, 2005b).

Intoxication

Cocaine is an inhibitor of monoamine transporters, especially dopamine but also norepinephrine and serotonin transporters. It disrupts the reuptake of dopamine from synapses, and the resultant increase in dopamine levels produces the desired feeling of euphoria (Stahl, 2008). There is also gregariousness, talkativeness, grandiosity, disinhibition and increased confidence and improved sense of mental acuity. The increase in noradrenaline leads to the stimulatory effects of cocaine, including tachycardia, hypertension, hyperthermia, mydriasis and insomnia (Wilson & De Miranda, 2001). Cocaine has a short duration of action of about 30 minutes (Weich, 2007). It has local anaesthetic properties and also causes local vasoconstriction when applied to mucous membranes – hence its continued use by otolaryngologists.

With excessive use of cocaine, the individual may experience undesirable effects such as anxiety, restlessness, irritability, agitation, stereotypical and repetitive behaviour and apprehension that may develop to suspiciousness, hypervigilance and paranoid behaviour. Cocaine-induced psychosis, which resembles an episode of paranoid schizophrenia, may last from a few days to weeks. There may be auditory hallucinations and sometimes tactile hallucinations. These effects are very similar to those of other stimulants, such as methamphetamine, but usually last for a shorter time.

Withdrawal

An individual may begin to experience symptoms of withdrawal within 24 hours of cessation, and these symptoms usually peak between two and four days after last use (Rastegar & Fingerhood, 2005b). Other symptoms include fatigue, sleep disturbances (from insomnia to hypersomnolence), headaches, tremor, muscle cramps and eating disturbances. Psychological effects include dysphoria, psychomotor agitation, apathy, social withdrawal, anhedonia and high levels of craving (Wilson & De Miranda, 2001).

Hallucinogens

The hallucinogens are a broad group of drugs, all with the ability through intoxication to alter a person's perceptions, thoughts and moods, and are often called the psychedelic drugs,

or psychotomimetics. The group includes lysergic acid diethylamide (LSD), phencyclidine (PCP, or angel dust), tetrahydrocannabinol (9 delta THC – one of the cannibinoids of cannabis), certain amphetamines (methylenedioxymethamphetamine – MDMA or ecstasy) and mescaline.

This is not a homogeneous class, and the hallucinogenic properties of its members are produced by their action on a variety of neurotransmitter systems, including 5-HT_2 receptor agonism (the classical hallucinogens), central dopamine stimulation (MDMA) and cholinergic and PCP receptors.

Classically, these agents should only produce changes in thought, perception and mood and should have minimal effect on intellectual ability or memory, should not sedate or cause excessive excitation, should cause no autonomic disarray or craving. However, problems can occur, and LSD is used as an example.

Dependence is described, but there are differences to the full dependence disorder. The hallucinogens are inclined to induce tolerance to euphoric and psychedelic effects but not to the autonomic/physiological effects. Craving is evident in some individuals but no apparent withdrawal syndrome. There is a hangover effect following hallucinogen use (particularly with MDMA), and this is characterised by insomnia, headaches, irritability, fatigue, drowsiness, headaches and muscle soreness.

Flashbacks (hallucinogen persisting perception disorders, or HPPD) are brief re-experiences of previous hallucinogenic intoxications in the absence of any current hallucinogenic usage. Such flashbacks can be quite disconcerting and distressing to the individual. They can be precipitated by stress, alcohol or insomnia.

LSD

LSD, first synthesised by Albert Hofmann in the Sandoz laboratories in 1936, is derived from the fungus ergot and is the prototype for most hallucinogens. Incredibly small doses, in the order of 25–100 micrograms, taken orally, are needed to have a hallucinogenic experience, often called an 'acid trip'. As a recreational drug, LSD was used extensively in the 1960s and 1970s. Its use in South Africa is very low, and barely registers in the statistics of drug units.

LSD acts on multiple sites in the brain, with an agonistic action at the presynaptic receptors for serotonin in the mid-brain, where neuronal activity is markedly decreased.

The individual's response to this drug depends on his or her mood, the company he or she is in, the dose and time of day, but usually results in a change of perception, with visual changes, mainly illusions but also hallucinations, that include changes in shape, movement, distance, colour and intensity of objects, sound and surroundings. These hallucinations are produced with a clear level of consciousness and a lack of confusion (Stahl, 2008). There are also strange changes in perception in that music can be seen or felt, and colours tasted or heard (synaesthesia). There are also distortions of body perception or image, with parts of one's body increasing in size or shrinking or separating from the rest. There are also changes to thinking, mood and perceptions of time, which were initially seen as positive benefits, allowing one to expand one's consciousness and connection with the universe and involving a very life-changing experience.

Physiologically, there can be increase in autonomic activity, as well as dilated pupils salivation, lacrimation, nausea and a fine tremor, incoordination and restlessness. Overdoses and fatalities are rare (Pechwick & Ungergleider, 2004)

For some, there is the penalty of intense fear and anxiety, and as intoxication escalates the individual may experience an acute confusional state (delirium) of disorientation and agitation. At times, frankly psychotic experiences may occur (the so-called bad trip), but with no apparent long-term brain damage (Stahl, 2008). Accidents can occur while intoxicated because of poor judgment and impaired decision-making abilities.

Cannabis (marijuana)

Cannabis is obtained from the plant *Cannabis sativa*. The psychoactive substances of cannabis are the cannabinoids, most importantly delta-9-tetrahydrocannabinol (THC). Cannabis can be smoked or ingested. If smoked, the effect is apparent within minutes and lasts 3–4 hours. If ingested, a larger dose is required to obtain the same effect; the onset of action is slower, but lasts longer. Due to most cannabinoids being fat-soluble, there can be a slow release of psychoactive substances from fatty tissue or the enterohepatic circulation, and the effect of cannabis may persist or recur for 12–24 hours. Cannibinoids can be detected in the urine for up to two weeks following cessation of the substance.

Intoxication

THC stimulates endogenous cannabinoid receptors to trigger the release of dopamine from the mesolimbic reward system (Stahl, 2008). Cannabis may result in a feeling of relaxation and a sense of wellbeing, although paradoxical anxiety may occur. It produces an altered perception of time (time being slowed down), distortions in visual, auditory and sensory perception and hallucinogenic effects such as depersonalisation and derealisation. Cannabis stimulates sympathetic activity, with tachycardia and hypertension, while at higher doses parasympathetic effects predominate, with bradycardia and orthostatic hypotension. Other physical effects include dry mouth, hunger and an injected conjunctival response. With regular cannabis use there may be impairment in neurocognitive function (short-term memory difficulties), and these impairments may persist for a day or longer after last use (Rastegar & Fingerhood, 2005d).

Individuals may experience adverse effects, such as anxiety, agitation and suspicion. With higher doses, and in susceptible individuals, psychosis may occur. There is a sudden onset of confusion generally associated with disorientation, disorganised speech, depersonalisation, delusions (most frequently paranoid) and hallucinations. This psychotic state may persist for a few hours to a few days. Regular cannabis use appears to confer an increased likelihood of developing schizophrenia in biologically susceptible individuals (Tucker, 2009; Degenhardt & Hall, 2006). Mood and anxiety disorders may also occur.

Amotivational syndrome has been described with long-term, heavy cannabis use. Individuals experience decreased drive, volition and ambition. They may have a shortened attention span and may be easily distracted. Individuals may also become introverted and exhibit poor interpersonal skills (Ghodse, 2002). Alternative views are that this disorder is actually the manifestation of underlying personality characteristics.

Cannabis toxicity is rare, even with consumption of large amounts. Individuals may experience drowsiness, ataxia and nausea and vomiting.

Withdrawal

With abstinence, regular users of cannabis may experience a flulike syndrome, which may include insomnia, anorexia, irritability, restlessness and drug craving.

Summary

What is evident is that substance use is a growing problem in South Africa and one which will impact on the mental and physical health of the user. In this chapter, we have covered the substance use disorders, looked at the criteria used to make this diagnosis and mentioned the direction in which we will view this spectrum from abuse to dependence in the future. This, together with the substance-induced disorders (intoxication, withdrawal, delirium, dementia, psychosis and mood disorders), will require that all mental health care providers be aware of these presentations and how they can impact on individuals, their family and community and their occupational functioning.

References

American Psychiatric Association. (2005). *Diagnostic and Statistical Manual of Mental Disorders*. DSM-IV Task Force and Working Group. 4th edition (text revision). Washington, DC: American Psychiatric Association.

Barr, A.M., Panenka, W.J., MacEwan, G.W., Thornton, A.E., Lang, D.J., Honer, W.G. & Lecomte, T. (2006). The need for speed: an update on methamphetamine addiction. *Journal of Psychiatry and Neuroscience*, 31(5):301–13.

Berman, A.H., Bergman, H., Palmstierna, T. & Schlyter, F. (2005). *DUDIT: Drug Use Disorders Identification Test*. Version 1. Stockholm: Karolinska Institutet.

Bush, K.R., Kivlahan, D.R., Davis, T.M., Dobie, D.J., Sporleder, J.L., Epler, A.J. & Bradley, K.A. (2003). The TWEAK is weak for alcohol screening among female Veterans Affairs outpatients. *Alcoholism: Clinical & Experimental Research*, 27(12):1971–78.

Caton, C.L., Drake, R.E., Hasin, D.S., Dominguez, B., Shrout, P.E., Samet, S. & Schanzer, B. (2005). Differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses. *Archives of General Psychiatry*, 62(2):137–45.

Degenhardt, L. & Hall, W. (2006). Is cannabis use a contributory cause of psychosis? *Canadian Journal of Psychiatry*, 51(9):556–65.

Dhalla, S. & Kopec, J.A. (2007). The CAGE questionnaire for alcohol misuse: a review of reliability and validity studies. *Clinical & Investigative Medicine*, 30(1):33–41.

Ewing, J.A. (1984). Detecting alcoholism. The CAGE questionnaire. *Journal of the American Medical Association*, 252(14):1905–907.

First, M.B., Spitzer, R.L., Gibbon, M. & Williams, J.B.W. (1994). *Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition* (SCID-I-P, version 2). New York: Biometrics Research Department, Columbia University.

Ghodse, H. (2002). Sedative-hypnotics. In H. Ghodse (ed.). *Drugs and Addictive Behaviour*. 3rd edition. Cambridge: Cambridge University Press.

Ghodse, H. (2002). Stimulant drugs. In H. Ghodse (ed.). *Drugs and Addictive Behaviour*. 3rd edition. Cambridge: Cambridge University Press; 117–21.

Grant, B.F., Stinson, F.S., Dawson, D.A., Chou, S.P., Dufour, M.C., Compton, W., Pickering, R.P. & Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. *Archives of General Psychiatry*, 61(8):807–16

Hasin, D., Hatzenbuehler, M.L., Keyes, K. & Ogburn, E. (2007). Diagnostic issues in substance use disorders. In J.B., Saunders, M.A., Schuckit, P.J. Sirovatka & D.A. Regier (eds). *Refining The Research Agenda For DSM-V: Substance Use Disorders – DSM-IV and ICD-10*. Arlington, VA: American Psychiatric Association.

Hasin, D.S., Trautman, K.D., Miele, G.M., Samet, S., Smith, M. & Endicott, J. (1996). Psychiatric Research Interview for Substance and Mental Disorders (PRISM): reliability for substance abusers. *American Journal of Psychiatry*, 153(9):1195–201.

Horsfall, J., Cleary, M., Hunt, G.E. & Walter, G. (2009). Psychosocial treatments for people with co-occurring severe mental illnesses and substance use disorders (dual diagnosis): a review of empirical evidence. *Harvard Review of Psychiatry*, 17(1):24–34.

Institute of Medicine (1990). *Broadening the Base of Treatment for Alcohol Problems*. Washington, DC: National Academy Press.

Kessler, R.C., Crum, R.M., Warner, L.A., Nelson, C.B., Schulenberg, J. & Anthony, J.C. (1997). Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the national Comorbidity Survey. *Archives of General Psychiatry*, 54(4):313–24.

Klatsky, A.L., Armstrong, M.A. & Friedman, G.D. (1992). Alcohol and mortality. *Annals of Internal Medicine*, 117(8):646–54.

Koob, G.F. (2009). Neurobiological substrates for the dark side of compulsivity in addiction. *Neuropharmacology*, 56(Suppl 1):18–31.

Kupfer, D.J. & Regier, D.A. (2010). American Psychiatric Association: DSM-5 development. Proposed revisions to substance related disorders. Available from: http://www.dsm5.org/proposedrevision/Pages/SubstanceUseandAddictiveDisorders.aspx; accessed 8 August 2011.

Mahoney, J.J., III, Kalechstein, A.D., De la Garza, R., II & Newton, T.F. (2008). Presence and persistence of psychotic symptoms in cocaine- versus methamphetamine-dependent participants. *American Journal on Addictions*, 17(2):83–98.

Mäkelä, K. (2004). Studies of the reliability and validity of the Addiction Severity Index. *Addiction*, 99(4):398–410.

Mathias, S., Lubman, D.I. & Hides, L. (2008). Substance-induced psychosis: a diagnostic conundrum. *Journal of Clinical Psychiatry*, 69(3):358–67.

McLellan, A.T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H. & Argeriou, M. (2008). Substance Use Disorders Measures: Addiction Severity Index (ASI). In J.A. Rush M.B. First & D. Blacker (eds). *Handbook of Psychiatric Measures*. 2nd edition. Washington, DC & London: American Psychiatric Publishing; 454–57.

McLellan, A.T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H. & Argeriou, M. (1992). The Fifth Edition of the Addiction Severity Index. *Journal of Substance Abuse Treatment*, 9(3):199–213.

Melega, W.P., Aleigh, M.J., Stout, D.B., Lacan, G., Sung-Cheng, H. & Phelps, M.E. (1997). Recovery of striatal dopamine function after acute amphetamine and methamphetamine induced neurotoxicity in the vervet monkey. *Brain Research*, 766(1–2):113–20.

Nunes, E. & Rounsaville, B.J. (2007). Comorbidity of substance use with depression and other mental disorders. In J.B. Saunders, M.A. Schuckit, P.J. Sirovatka & D.A. Regier (eds). *Diagnostic Issues in Substance Use Disorders. Refining the Research Agenda for DSM-V*. Arlington, VA: American Psychiatric Publishing.

Parry, C.D.H. (2005). South Africa: alcohol today. *Addiction*, 100(4):426–29

Pechwick, R.N. & Ungerleider, J.T. (2004). Hallucinogens. In M. Galanter & H. Kleber (eds). *Textbook of Substance Use Treatment*. 3rd edition. Arlington, VA: American Psychiatric Publishing.

Plüddemann, A., Parry, C., Dada, S., Kader, R., Parker, J., Lewis, I., Temmingh, H., De Clercq, C. & Van Heerden, S. (June 2009). Monitoring the prevalence of methamphetamine related presentations at psychiatric hospitals in Cape Town. Personal communication.

Raimo, E.B. & Schukit, M.A. (1998). Alcohol dependence and mood disorders. *Addictive Behaviors*, 23(6):933–46.

Rastegar, D. & Fingerhood, M. (eds). (2005b). Cocaine and other stimulants. In *Addiction Medicine: An Evidence-Based Handbook*. Philadelphia: Lippincott Williams & Wilkens; 143–63.

Rastegar, D. & Fingerhood, M. (eds). (2005d). Marijuana. In *Addiction Medicine: An Evidence-Based Handbook*. Philadelphia: Lippincott Williams & Wilkens; 179–87.

Rastegar, D. & Fingerhood, M. (eds). (2005c). Opioids. In *Addiction Medicine: An Evidence-Based Handbook*. Philadelphia: Lippincott Williams & Wilkens; 89–23.

Rastegar, D. & Fingerhood, M. (eds). (2005a). Sedative-hypnotics. In *Addiction Medicine: An Evidence-Based Handbook*. Philadelphia: Lippincott Williams & Wilkens; 76–87.

Reinert D.F. & Allen, J.P. (2002). The Alcohol Use Disorders Identification Test (AUDIT): a review of recent research. *Alcoholism: Clinical & Experimental Research*, 26(2):272–79.

Ross S. (2008). The mentally ill substance abuser. In M. Galanter & H. Kleber (eds). *Textbook of Substance Use Treatment*. 4th edition. Washington, DC & London: American Psychiatric Publishing.

Russell, M., Czarnecki, D.M., Cowan, R., McPherson, E. & Mudar, P.J. (1991). Measures of maternal alcohol use as predictors of development in early childhood. *Alcoholism: Clinical & Experimental Research*, 15(6):991–1000.

SACENDU. (2006). Alcohol and drug abuse trends: January–June 2006 (Phase 20). Cape Town: SACENDU, ADURA, MRC.

Saunders, J.B., Aasland, O.G, Babor, T.F., De la Fuente, J. & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption–II. *Addiction*, 88(6):791–804.

Saunders, J.B., Schuckit, M.A., Sirovatka, P.J. & Regier, D.A. (2007). Diagnostic issues in substance use disorders. In J.B. Saunders, M.A. Schuckit, P.J. Sirovatka & D.A. Regier

(eds). *Diagnostic Issues in Substance Use Disorders. Refining the Research Agenda for DSM-V*. Arlington, VA: American Psychiatric Publishing.

Selzer, M.L. (1971). The Michigan alcoholism screening test: the quest for a new diagnostic instrument. *American Journal of Psychiatry*, 127(12):1653–58.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, 59(Suppl 20):22–33.

Skinner, H.A. (1982). The drug abuse screening test. *Addictive Behaviors*, 7(4):363–71.

Smit, J., Van den Berg, C.E., Bekker, L.G., Seedat, S.& Stein, D.J. (2006). Translation and cross-cultural adaptation of a mental health battery in an African setting. *African Health Sciences*, 6(4):215–22.

Stahl, S. (2008). Disorders of reward, drug abuse, and their treatment. In S. Stahl (ed.). *Stahl's Essential Psychopharmacology*. 3rd edition. New York: Cambridge University Press; 977–93.

Selzer, M.L. (2008). Substance use disorder measures: Michigan Alcoholism Screening Test (MAST). In J.A. Rush M.B. First & D. Blacker (eds). *Handbook of Psychiatric Measures*. 2nd edition. Washington, DC & London: American Psychiatric Publishing; 450-51.

Taylor, D., Paton, C. & Kerwin, R. (eds). (2007). Substance misuse. In *The South London and Maudsley NHS Foundation Trust & Oxleas NHS Foundation Trust. Prescribing Guidelines*. 9th edition. London: Informa Healthcare; 302–52.

Torrens, M., Serrano, D., Astals, M., Perez-Dominguez, G. & Martin-Santos, R. (2004). Diagnosing comorbid psychiatric disorders in substance abusers: validity of the Spanish versions of the Psychiatric Research Interview for Substance and Mental Disorders and the Structured Clinical Interview for DSM-IV. *American Journal of Psychiatry*, 161(7):1231–37.

Tucker, P. (2009). Substance misuse and early psychosis. *Australasian Psychiatry*, 17(4):291–94.

Weich, L. (2007). Alcohol and other substance-abuse disorders. In S.E. Baumann (ed.). *Primary Health Care Psychiatry*. Cape Town: Juta & Co.; 290–319.

Weich, L. & Pienaar, W. (2009). Occurrence of comorbid substance use disorders among acute psychiatric inpatients at Stikland Hospital in the Western Cape, South Africa. *African Journal of Psychiatry* (Johannesburg), 12(3):213–17.

Wilson, D. & De Miranda, S. (2001). Other substance-related disorders. In B. Robertson, C. Allwood & C. Gagiano (eds). *Textbook of Psychiatry for Southern Africa*. Cape Town: Oxford University Press; 196–217.

World Health Organization (WHO). (1992). *WHO ICD-10 Classification of Mental and Behavorial Disorders. Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization.

Xiong, G.L. & Daubert, G.P. (2009). eMedicine Psychiatry: Wernicke-Korsakoffs Syndrome. Available from: http://emedicine.medscape.com/article/288379-overview; accessed 8 August 2011.

3 Developmental consequences of prenatal drug and alcohol exposure

Colleen M. Adnams

The increase in substance abuse in pregnancy over past decades has rendered large numbers of infants and children at risk for the adverse consequences of prenatal exposure to those substances. Although the effects of legal and illegal addictive substances are well described in adults, less is known about the short- and long-term effects of these substances on the developing fetus. There is, however, internationally a growing body of information on prenatal exposure to substances, including cocaine, opiates, tobacco, marijuana and amphetamines. In a recent literature review, Keegan et al (2010) reported that approximately 225 000 infants per year in the United States are exposed prenatally to illicit substances. Although all of the abovementioned substances are misused in the general population in South Africa, in particular marijuana and methamphetamine, there is a paucity of published data on the prevalence of use of these substances during pregnancy. Furthermore, there is no available published data on the neurodevelopmental outcomes of prenatally exposed infants and children.

Compared to other addictive substances, there is a large body of information on alcohol consumption by women in pregnancy. Women who drink alcohol while pregnant are at high risk of giving birth to children with clinical defects and developmental disabilities resulting from alcohol injury to the unborn child. Injuries caused by alcohol to the developing fetus may result in a constellation of features, consisting of poor growth, distinct facial morphology, physical defects and cognitive and behavioural developmental delays and disabilities. The cognitive and behavioural manifestations are by far the most commonly noticeable features and have the greatest negative impact. Since the first published reports on fetal alcohol syndrome (FAS), (Jones & Smith 1973; Jones et al, 1973), the prevalence of FAS and neurobehavioural outcomes of individuals exposed prenatally to alcohol have been extensively delineated. The first reports of FAS in the medical literature in South Africa were published in 1978 (Beyers & Moosa 1978; Hayden & Nelson 1978).

Prenatal exposure to substances other than alochol

Cocaine

Most clinical descriptions of, and research on, outcomes in prenatal substance exposure have focused on maternal use of cocaine. Complications of use of cocaine in pregnancy include spontaneous abortion, preterm birth, placental abruption and congenital anomalies and in the neonatal period, feeding and arousal problems and seizures (Keegan et al, 2010). Data on the long-term effects of prenatal cocaine exposure indicate there are specific problems of cognition, language and behaviour, including attentional deficits (Lester & Lagasse, 2010).

Opioids

The most frequently abused opioids are heroin and methadone, and thus the literature on prenatal opioid exposure focuses on these substances. Methadone is prescribed as a treatment substitute for heroin addiction. The major effects of prenatal exposure to opioids manifest in the neonatal period when there is a risk of withdrawal symptoms. The so-called neonatal abstinence syndrome is well described. What is less clear is the long-term effect on behaviour and cognition. Although a range of deficits in cognition, memory, attention, perception and behaviour are described, it is difficult to separate these effects from the overall influence of an adverse postnatal environment (Davies & Bledsoe, 2005). Lester et al (2009) tested a structural equation model to assess whether neurobehavioural dysregulation in infants who were prenatally exposed to cocaine and other substances would predict for externalising and internalising behaviour problems at seven years of age. The authors demonstrated a direct teratogenic effect of substance abuse on behaviour at seven years, as well as indirect effects that were mediated by early behavioural dysregulation.

Tobacco

Worldwide, tobacco use in pregnancy is common. Apart from a consistently demonstrated relationship between tobacco and pregnancy and birth complications, including fetal death, preterm birth and low birth weight, long-term behaviour problems in children are also described. What has not been ascertained with certainty is whether the tobacco-behaviour relationship is causal, or whether the behaviour occurs in the context of other family and environmental factors that increase the risk for child health and developmental problems in childhood (Roza et al, 2009). On balance, evidence suggests a causal link between adverse cognitive and behavioural outcomes in children and exposure to tobacco smoke in pregnancy, in particular attention deficit hyperactivity disorder (ADHD)-like symptoms (Olds, 1997), externalising behaviours (Williams et al, 1998), visual-motor coordination and interhemispheric processing speed (Willford et al, 2010) and small decrements on academic performance in adolescence (O'Callaghan et al, 2010).

Marijuana

Marijuana may cause transient growth delay in the developing fetus and withdrawal symptoms in the neonatal period (Davies & Bledsoe, 2005). Longer term, there is an association with subtle effects on higher-level executive functioning (Fried, 2002), attention (Goldschmidt et al, 2000), learning and memory (Richardson et al, 2002) and processing speed and visual-motor coordination (Willford et al, 2010).

Methamphetamine

Methamphetamine abuse, a worldwide problem, is epidemic in South Africa. The prevalence of methamphetamine abuse in pregnancy in South Africa is unknown, but is likely to be high, given the extent of the epidemic in the population of child-bearing age, the low costs of acquiring the drug and its behavioural effects. A small body of research in other countries is delineating the fetal and longer term effects of

prenatal methamphetamine exposure. Early studies suggested the developmental effects of methamphetamine may be similar to those of cocaine, with an increase in preterm birth and placental abruption (Eriksson et al, 1978). Fetal growth has been shown to be inhibited, resulting in low birth weight (Smith et al, 2003; Nguyen et al, 2010). In a multisite cross-cultural study in the United States and New Zealand, Lagasse et al (2011) reported neonatal neurobehavioural patterns of low arousal, gross motor in-coordination and increased stress.

In older children, behaviour problems and hyperactivity (Chang et al, 2004) and specific difficulties with visual integration, verbal and spatial memory and attention (Billing et al, 1994) and verbal memory (Lu et al, 2009) have been described. Chang (2007) reviewed the structural and metabolic changes in children with prenatal methamphetamine exposure. Using structural MRI brain imaging techniques to investigate the brain/behaviour relationship in adolescents whose mothers abused methamphetamine during pregnancy, Sowell et al (2010) documented volume changes in several areas, including the caudate and cingulate nucleus. In individuals prenatally exposed to methamphetamine alone, the volume of the caudate nucleus, which is associated with learning, memory, motor control and punishment and reward, showed greater reductions in individuals exposed to methamphetamine alone than those with alcohol exposure. In the methamphetamine-exposed group, there was a negative correlation between caudate volume and full scale IQ, suggesting a more severe cognitive outcome in prenatal methamphetamine exposure than alcohol exposure in the study population. In addition, in methamphetamine-exposed children, an abnormal volume increase was noted in the cingulate cortex, which is associated with control and conflict resolution. Prenatal exposure to both alcohol and methamphetamine resulted in brain volume changes that were more severe than in the case of either drug alone, suggesting greater brain injury in children of mothers who abused both substances in pregnancy. These study findings warrant replication in South African populations in the light of the fact that studies on fetal alcohol spectrum disorder (FASD) in South Africa involve cohorts of children on the more severe end of the FASD spectrum than those cohorts studied in Western countries. The mounting evidence from studies of prenatal methamphetamine exposure has important implications for interventions aimed at South African women of child-bearing age who abuse methamphetamine and who may also co-abuse methamphetamine and alcohol.

Prenatal exposure to alcohol

Fetal alcohol spectrum disorder (FASD)

The broad range of effects of prenatal exposure to alcohol constitutes a continuum. FASD is an umbrella term that has been used to describe the broader range of effects that can occur in an individual whose mother drank alcohol during pregnancy. The range encompasses a continuum of mild to severe physical, cognitive and behavioural effects. This term applies especially when a diagnosis of FAS is not made.

FASD is well recognised as the most important preventable cause of intellectual disability worldwide, and as such constitutes a major global public health problem. The term 'FASD' is not intended for use as a clinical diagnosis. The aim of the wider

terminology is to contribute toward recognition of the social, treatment and service needs in individuals with the disorder. Within the FASD spectrum there are four recognised diagnostic categories:

1) **Fetal alcohol syndrome (FAS)** represents the severe end of the FASD spectrum, in which there is physical growth retardation (height, weight and head circumference), characteristic facial dysmorphology, evidence of central nervous system (CNS) neurobehavioural deficits and a positive or suspected history of alcohol in pregnancy
2) **Partial FAS (PFAS)** is diagnosed when full criteria for FAS are not met, with or without confirmation of prenatal alcohol exposure
3) **Alcohol-related neurodevelopmental deficit (ARND)** criteria may include normal growth but cognitive and/or neurobehavioural deficits in the context of prenatal alcohol exposure that are not explained by any other cause
4) **Alcohol-related birth defect (ARBD)** describes physical birth defects caused by alcohol injury during fetal development. The detailed diagnostic criteria are summarised by Hoyme et al (2005).

Mechanisms of alcohol injury in the developing fetus

Alcohol is a potent teratogen to the developing fetus, and exposure to moderate to high concentrations of alcohol causes permanent and multisystem damage. Alcohol in maternal blood freely crosses the placenta into the blood and other tissues of the developing embryo or fetus. Numerous mechanisms contribute to the damaging effects of alcohol in the developing fetus. Although FASD is a multisystem disorder, the developing central nervous system is the most vulnerable to alcohol injury. The damaging mechanisms through which alcohol may exert its effects occur simultaneously or consecutively and result in cell death by necrosis or apoptosis. Animal models and tissue-culture experiments continue to elucidate injury mechanisms, which include increased oxidative stress, mitochondrial and glial cell damage, impaired cellular chemical messenger, neurotransmitter and cellular energy transport systems and alteration in genes and gene regulation (Goodlett & Horn, 2001).

There is a dose-response association between alcohol exposure and fetal damage. Thus the type and extent of alcohol injury to the fetus is related to volume and frequency of alcohol consumed during pregnancy, as well as the duration of exposure and the period in pregnancy during which the mother drinks, with higher exposure resulting in greater damage and lower levels of exposure resulting in more subtle effects. Binge-type drinking, which results in a high maternal blood alcohol concentration, is associated with particularly severe developmental deficits. It is thought that the effect of withdrawal on the fetus between maternal binges is also particularly deleterious at a fetal cellular level. A threshold or safe level of alcohol concentration for unimpaired development of the fetus in pregnancy has not been established. The first trimester of pregnancy, during which the CNS develops and differentiates rapidly, is a critical period for injury. Certain genetic factors may be protective. In the mixed-ancestry population of the Western Cape province, the alcohol dehydrogenase-2*2 allele is associated with decreased prevalence of fetal alcohol syndrome (Viljoen et al, 2001), and the maternal ADH1B*3 allele is protective for infant and child outcomes at 7.5 years (Jacobson et al, 2006).

Epidemiology of FASD

Prevalence

Most international prevalence studies have focused on high-risk or geographically localised populations. In a population estimate, 1% of United States newborns was estimated to fall into the spectrum of fetal alcohol disorders (Sampson et al, 1997). May et al (2006) reported a relatively high prevalence of FAS in a province of Italy, of 3.7 to 7.4 per 1 000 school entry-level children. Including the diagnosis of PFAS and ARND, the rate of FASD was estimated to be 20.3 to 40.5 per 1 000 or between 2.3 and 4.1% of all children. This represents the highest population-based prevalence of FASD reported in the Western world. Although this result reflects improved measures of ascertainment of the FASD spectrum, the question is raised whether FASD is more common than previously estimated in the Western world (May et al, 2006).

In the first South African population-based study on the prevalence of the full spectrum of disorders, May et al (2007) used the same revised Institute of Medicine diagnostic criteria for FASD (Hoyme et al, 2005) and case ascertainment as in the Italy population epidemiology study in a high-risk community in the Western Cape province. The authors reported a prevalence of FAS and PFAS of 68–89.2 per 1 000. Previous studies in the same community yielded slightly lower FAS prevalence figures, but of the same order (May et al, 2000; Viljoen et al, 2005). However, in these earlier studies the full FASD spectrum, including PFAS and ARND, was not measured. In two other high-risk regions in the Northern Cape province, Urban et al (2008) reported an even higher prevalence of FAS (overall 67.2 per 1 000) and FAS and PFAS combined (119.4 per 1 000 and 74.7 per 1 000, respectively). These South African prevalence figures represent the highest reported in the world. High-prevalence figures of FAS were also reported in an urban area in Gauteng province (Viljoen & Craig, 2003). Notably, in comparison with Western and European country populations studied, a far greater proportion of South African children on the FASD spectrum were diagnosed with FAS, thus falling on the most severe end of the FASD spectrum more often than those children with FASD in Western studies.

Historical context of FASD in South Africa

The causes of women drinking in pregnancy are complex and involve historical, social and cultural factors. Undoubtedly the now-outlawed 'dop' system of payment of agricultural and other labourers with liquor played a key contributory role to present patterns of alcohol abuse (London et al, 1998; London, 1999). In order to interpret the complexities of FASD in South Africa, this condition needs to be seen in the context of both the global burden of substance abuse and the factors influencing present-day South Africa.

Maternal risk factors for FASD

Several studies have elucidated risk factors for FASD in the South African population. There is characteristically a pattern of binge drinking, and in the Western Cape province community studied, severe episodic drinking on weekends among mothers of children with FAS and PFAS accounted for 96% of all alcohol consumed (May et al, 2007). Maternal risk factors include low socioeconomic status, low education, lower body mass, smoking and

higher age and parity (Viljoen et al, 2002; May et al, 2004; May et al, 2005; Urban et al, 2008). Most of these risk factors are similar to those documented in other international studies.

Burden of disease estimates of FAS

The South African burden-of-disease estimates of 2000 included the impact of FAS (Schneider et al, 2007). FAS (5.5%) was the fourth-largest contributor to alcohol-attributable disability-adjusted life-years (DALYs) for persons, after interpersonal violence (39%), alcohol dependence-use disorders (14.7%) and road traffic injuries (14.3%). A FAS prevalence of 14 per 1 000 at birth for the general population was used, and there was no adjustment for FAS-related death. Given the higher prevalence rates of FAS and FASD reported in South African epidemiology studies, and the fact that this burden of disease study represents FAS and not the FASD continuum, it is likely that the study considerably underestimates the burden of disease of FASD.

There has been little research on the cost of FASD in South Africa. A study conducted in the Western Cape estimated that the total average annual healthcare cost to the province per 0–12-year-old child with FASD was US$1 039, while the total annual societal cost of FASD for the Western Cape was US$70 960 053 (Credé et al, 2011). These results provide evidence of the considerable burden of FASD on the Western Cape economy and healthcare system and have significant implications for FASD prevention.

Neurobehavioural manifestations of FASD

Because of differences in the dose and timing of prenatal alcohol exposure, and of individual susceptibility and postnatal influences, the clinical manifestations are varied and complex. Although a core neurobehavioural phenotype in FASD remains to be clearly delineated, patterns of deficits in cognition and behaviour have been well described. A key question is whether there is a unique cognitive-behavioural functioning and behavioural phenotype in FASD.

Researchers have consistently found deficits in general intelligence, learning, social adaptation and behaviour in FASD. The average IQ of affected children is in the borderline and mild intellectual disability range. However, it is now known that the damage done to the developing brain may result in specific neurobehavioural problems in the face of normal general intelligence (Hoyme et al, 2005). Specific problems independent of general intelligence may occur in the areas of language, learning and memory, attention and speed of information processing, number processing, visuo-spatial skills and motor skills. Other problems include deficits in abstract thinking, executive function and planning and problems with response inhibition, hyperactivity, impulsivity and behaviour control. Children with FASD also have problems with adaptive behaviour and emotional functioning. All of these deficits lead to problems with academic, classroom and social performance. In general, children with FASD show greater impairment on complex tasks and adaptive demands than on simple tasks and demands. For detailed reviews of the neurobehavioral findings in FASD, see Riley et al (2005) and Kodituwakku (2007).

Similar patterns of cognitive and behavioural deficits have been confirmed in South African studies of children with FASD. Deficits are reported in general intelligence (May

et al, 2000; 2007; Adnams et al, 2001; Viljoen et al, 2005; Urban et al, 2008), language, phonological working memory, reading and writing (Adnams et al, 2001; Adnams et al, 2007), executive function (Kodituwakku et al, 2006), processing speed (Burden et al, 2009) and number processing (Meintjes et al, 2010). Studies in South African infants show early response deficits in biobehavioural arousal to pain stimuli (Oberlander et al, 2010), eye blink conditioning (Jacobson et al, 2008) and visual acuity (Carter et al, 2005).

While increases in volumes and frequency of prenatal alcohol exposure result in progressively more severe cognitive and behavioural deficits, there is uncertainty about the safe lower threshold. There is conflicting evidence for more subtle effects at lower alcohol exposure levels, not least because of a lack of standardisation of what constitutes low exposure and problems with both reporting and recording of maternal alcohol intake. A number of studies have demonstrated that lower levels of alcohol consumption by a pregnant mother still place her fetus at risk of a neurobehavioural impairment (Jacobson & Jacobson, 1999; Sampson et al, 1997). Sayal et al (2009) reported from a United Kingdom longitudinal population-based study that any episode of consumption of four drinks per day during pregnancy is associated with problems of hyperactivity and attention at age 6.75 years, in the absence of moderate daily levels of drinking.

The establishment of a causal relationship between prenatal alcohol exposure and neurobehavioural outcomes is confounded by genetic, environmental and psychosocial factors. When compared to research cohorts from developed Western countries, for similar prenatal exposure, many South African children with FASD are worse affected and have lower general cognitive functioning. This illustrates the influence of suboptimal early biological, environmental and other factors that may exert a negative effect on child developmental outcomes in developing countries (Grantham-McGregor et al, 2007; Adnams, 2010). In addition, in low-resource settings, cognitive and behavioural difficulties are more likely to be unrecognised, with the result that affected children's special developmental needs may be unmet and, in this way, their difficulties exacerbated.

Brain changes in FASD

The advent of neuroimaging techniques has enhanced the ability to examine neuro-anatomical correlates of brain structure and function in FASD. Apart from the overall decrease in brain size in moderately and severely exposed individuals, there is evidence for specific morphological changes and abnormal changes in shape in vulnerable brain areas, including the frontal and parietal lobes, cerebellar vermis, corpus callosum and caudate nucleus. A systematic review of brain structural and functional changes is provided by Spadoni et al (2007). In a series of studies, Bookstein et al (2001, 2002a, 2002b) documented changes in the corpus callosum in adults with prenatal alcohol exposure. There was a correlation with corpus callosum size and shape with neurocognitive function in affected individuals. Sowell et al (2002a, 2002b, 2008) used brain mapping techniques to demonstrate an increase in grey matter and a decrease in white matter in the perisylvian cortex of the temporal and parietal lobes and white matter changes in the splenium of the corpus callosum in adolescents with prenatal alcohol exposure. Changes in white matter in the splenium correlated with visual motor integration deficits. O'Hare et al (2009) reported a significant association between corpus frontal lobe changes and verbal learning. The ability to locate anatomical sites of

brain function and dysfunction related to specific cognitive tasks (ie, cognitive strengths and weaknesses) provides novel opportunities for evidence-based neurobehavioural and cognitive interventions in FASD.

Family issues and mental health in FASD

A high prevalence of mental illness and poor social adjustment is described across the life span in individuals with prenatal exposure to alcohol, including in infancy, early and middle childhood, adolescence and adulthood (O'Connor et al, 2002; O'Connor & Paley, 2006, 2009; Streissguth & O'Malley, 2000; Barr et al, 2006). Depression is commonly described throughout the life span, with psychiatric illness increasing from adolescence. In South African adolescents with FASD, there was an increase in both internalising and externalising behaviours (Adnams et al, unpublished data).

Having a child with FASD affects the entire family, and maternal alcohol abuse in itself affects the mother's ability to care for children. There is a higher rate of intergenerational drinking in families with FASD, and many parents of children with FASD were themselves prenatally exposed to alcohol. Consistent with international literature, South African studies (May et al, 2005; Viljoen et al, 2002) demonstrated that mothers of children with FASD were themselves frequently raised in an environment where heavy maternal drinking was prevalent. Parents with FASD demonstrate similar cognitive and behavioural difficulties to their children, and this manifests in further problems of parenting. There is a higher rate of foster and adoptive care among children with FASD, and among all children who are fostered or adopted there is also a greater risk of FASD. Although there are no data in this regard in South Africa, of a group of 71 children adopted in Sweden from Eastern Europe, 30% were found to have FAS and 52% FASD (Landgren et al, 2010).

Interventions in children and adults with FASD

Current knowledge of neurocognitive deficits and relative strengths in FASD is sufficient to provide a base for development of appropriate interventions. However, there is a paucity of research-based interventions for children and youth with FASD and few systematic outcomes studies of educational or behavioural intervention programmes exist. Interventions in FASD have been previously reviewed by Premji et al (2007) and Peadon et al (2009). Studies have reported improvements following cognitive and psycho-social approaches to interventions in a range of areas, including family functioning, social skills, language and literacy and mathematics.

Younger children with FASD have behavioural problems such as impulsivity, hyperactivity and deficits in concentration and attention that constellate a major problem in the formal educational setting. Formal education may often be a negative experience associated with low self-esteem and school failure, which in turn places demands on educational and other resources. In a pilot intervention study addressing classroom self-regulation in a small group of South African Grade 3 children, we observed an improvement in self-efficacy and classroom behaviour (Riley et al, 2003). In another systematic classroom-based intervention in similarly-aged South African children with FASD, a language and literacy programme

resulted in significant improvements in the targeted areas of learning compared to control children with FASD and a non-exposed control group (Adnams et al, 2007). The deficits in FASD are thus not fixed and are ameliorable. Since the majority of children with FASD have borderline/mild intellectual disability, they require additional specialised educational support. Further research is required to identify effective strategies for interventions in persons with FASD across the life span.

Policies and services for FASD in South Africa

The national impact and cost of FASD in South Africa has not been systematically addressed, yet must be staggeringly high, taking into account the magnitude of its prevalence and nature of neurodevelopmental and social outcomes. There is cost data from only one province. The direct and indirect costs impact significantly on the health, education, social welfare, labour and criminal justice sectors, as well as on individuals, families, communities and the broader society. In spite of this, there are no policies that directly address FASD in South Africa and no national or provincial programmes that comprehensively address prevention, identification or interventions (Randall-Mkosi et al, 2008). The same deficit applies at the service level, where, across all sectors and disciplines, there is little expertise in recognition, assessment and management of FASD.

In a situational and gap analysis of FASD in South Africa, Randall-Mkosi et al (2008) provided a set of recommendations on the prevention of FASD and support for those with FASD. The authors called for a national goal to reduce the prevalence of FASD and the impact of the primary and secondary disabilities of FASD on individuals and society. The strategies proposed to achieve these goals through leadership at national governmental level, establishment of guidelines on screening and identification and a minimal package of services for persons with FASD and provision of adequate budgetary and resource commitment from all sectors. The recommendations included surveillance, detection and intervention with women at risk for alcohol-exposed pregnancy and the training of health and other professionals in identification and care of at-risk women and affected individuals. Finally, the recommendations addressed the need for public education, awareness, advocacy and research.

Conclusion

While rates of abuse of most substances harmful to the fetus are unknown in South Africa, it is likely that, for commonly abused substances, the prevalence is high. FASD is a major public health problem in South Africa, with a considerable impact on society. The prevalence and impact of prenatal exposure to methamphetamine warrants investigation. Advances in brain-behaviour science present an unprecedented opportunity for further understanding of the genetic, brain structural, neurobehavioural and neuro-anatomical tenets that underlie developmental outcomes of prenatal substance exposure. In turn, knowledge acquired in this way can hopefully make a meaningful contribution to evidence-based, broader approaches through policy, public health and prevention/intervention strategies.

References

Adnams, C.M. (2010). Perspectives of intellectual disability in South Africa: epidemiology, policy, services for children and adults. *Current Opinion in Psychiatry*, 23(5):436–40.

Adnams, C.M., Kodituwakku, P.W., Hay, A., Molteno, C.D., Viljoen, D. & May, P.A. (2001). Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcoholism: Clinical & Experimental Research*, 25(4): 557–62.

Adnams, C.M., Sorour, P., Kalberg, W.O., Kodituwakku, P., Perold, M.D., Kotze, A., September, S., Castle, B., Gossage, J. & May, P.A. (2007). Language and literacy outcomes from a pilot intervention study for children with fetal alcohol spectrum disorders in South Africa. *Alcohol*, 41(6):403–14.

Barr, H.M., Bookstein, F.L., O'Malley, K.D., Connor, P.D., Huggins, J.E. & Streissguth, A.P. (2006). Binge drinking during pregnancy as a predictor of psychiatric disorders on the Structured Clinical Interview for DSM-IV in young adult offspring. *American Journal of Psychiatry*, 163(6):1061–65.

Beyers, N. & Moosa, A. (1978). The fetal alcohol syndrome. *South African Medical Journal*, 54:575–78.

Billing, L., Eriksson, M., Jonsson, B., Steneroth, G. & Zetterström, R. (1994). The influence of environmental factors on behavioural problems in 8-year-old children exposed to methamphetamine during fetal life. *Child Abuse & Neglect*, 18(1):3–9.

Bookstein, F.L., Sampson, P.D., Connor, P.D. & Streissguth, A.P. (2002a). Midline corpus callosum is a neuroanatomical focus of fetal alcohol damage. *The Anatomical Record*, 269(3):162–74.

Bookstein, F.L., Streissguth, A.P., Sampson, P.D. & Connor, P.D. (2001). Geometric morphometrics of corpus callosum and subcortical structures in the fetal-alcohol-affected brain. *Teratology*, 64(1):4–32

Bookstein, F.L., Streissguth, A.P., Sampson, P.D., Connor, P.D. & Barr, H.M. (2002b). Corpus c-allosum shape and neuropsychological deficits in adult males with heavy fetal alcohol exposure. *NeuroImage*, 15(1):233–51.

Burden, M.J., Andrew, C., Saint-Amour, D., Meintjes, E.M., Molteno, C.D., Hoyme, H.E., Robinson, L.K., Khaole, N., Nelson, C.A., Jacobson, J.L. & Jacobson S.W. (2009). The effects of fetal alcohol syndrome on response execution and inhibition: an event-related potential study. *Alcoholism: Clinical & Experimental Research*, 33(11):1994–2004.

Carter, R.C., Jacobson, S.W., Molteno, C.D., Chiodo, L.M., Viljoen, D. & Jacobson, J.L. (2005). Effects of prenatal alcohol exposure on infant visual acuity. *Journal of Pediatrics*, 147(4):473–79.

Chang, L., Alicata, D., Ernst, T. & Volkow, N. (2007). Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. *Addiction*, 102(Suppl. 1):16–32.

Chang, L., Smith, L.M., LoPresti, C., Yonekura, M.L., Kuo, J., Walot, I. & Ernst, T. (2004). Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatry Research*, 132(2):95–106.

Credé, S., Adnams, C.M., Sinanovic, E. & London, L. (2011). The utilization of health care services by children with foetal alcohol syndrome in the Western Cape, South Africa. *Drug & Alcohol Dependence*, 115(3):175–82

Davies, J.K. & Bledsoe, J.M. (2005). Prenatal alcohol and drug exposures in adoption. *Pediatric Clinics of North America*, 52(5):1369–93, vii.

Eriksson, M., Larsson, G., Winbladh, B. & Zetterström, R. (1978). The influence of amphetamine addiction on pregnancy and the newborn infant. *Acta Paediatrica Scandinavica*, 67(1):95–99.

Fried, P.A. (2002). Adolescents prenatally exposed to marijuana: examination of facets of complex behaviors and comparisons with the influence of in utero cigarettes. *The Journal of Clinical Pharmacology*, 42(11 Suppl.):97S–102S.

Goldschmidt, L., Day, N.L. & Richardson, G.A. (2000). Effects of prenatal marijuana exposure on childbehavior problems at age 10. *Neurotoxicology and Teratology*, 22(3):325–36.

Goodlett, C.R. & Horn, K.H. (2001). Mechanisms of alcohol-induced damage to the developing nervous system. *Alcohol Research & Health*, 25(3):175–84

Grantham-McGregor, S., Cheung, Y.B., Cueto, S., Glewwe, P., Richter, L., Strupp, B. & International Child Development Steering Group. (2007). Developmental potential in the first 5 years for children in developing countries. *Lancet*, 369(9555):60–70.

Hayden, M.R. & Nelson, M.M. (1978). The fetal alcohol syndrome. *South African Medical Journal*, 54:571–74.

Hoyme, H.E., May, P.A., Kalberg, W.O., Kodituwakku, P., Gossage, J.P., Trujillo, P.M., Buckley, D.G., Miller, J.H., Aragon, A.S., Khaole, N., Viljoen, D.L., Jones, K.L. & Robinson, L.K. (2005). A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics*, 115(1):39–47.

Jacobson, J.L. & Jacobson, S.W. (1999). Drinking moderately and pregnancy. Effects on child development. *Alcohol Research & Health*, 23(1):25–30.

Jacobson, S.W., Carr, L.G., Croxford, J., Sokol, R.J., Li, T.K. & Jacobson, J.L. (2006). Protective effects of the alcohol dehydrogenase-ADH1B allele in children exposed to alcohol during pregnancy. *Journal of Pediatrics*, 148(1):30–37.

Jacobson, S.W., Stanton, M.E., Molteno, C.D., Burden, M.J., Fuller, D.S., Hoyme, H.E., Robinson, L.K., Khaole, N. & Jacobson, J.L. (2008). Impaired eyeblink conditioning in children with fetal alcohol syndrome. *Alcoholism: Clinical & Experimental Research*, 32(2):365–72.

Jones, K.L. & Smith, D.W. (1973). Recognition of the fetal alcohol syndrome in early infancy. *Lancet*, 302(7836):999–1001.

Jones, K.L., Smith, D.W., Ulleland, C.N. & Streissguth, A.P. (1973). Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet*, 1(7815):1267–71.

Keegan, J., Parva, M., Finnegan, M., Gerson, A. & Belden, M. (2010). Addiction in pregnancy. *Journal of Addictive Diseases*, 29(2):175–91.

Kodituwakku, P.W. (2007). Defining the behavioral phenotype in children with fetal alcohol spectrum disorders: a review. *Neuroscience & Biobehavioral Reviews*, 31(2):192–201.

Kodituwakku, P.W., Adnams, C.M., Hay, A., Kitching, A.E., Burger, E., Kalberg, W.O., Viljoen, D.L. & May, P.A. (2006). Letter and category fluency in children with fetal alcohol syndrome from a community in South Africa. *Journal of Studies on Alcohol*, 67(4):502–509.

Lagasse, L.L., Wouldes, T., Newman, E., Smith, L.M., Shah, R.Z., Derauf, C., Huestis, M.A., Arria, A.M., Grotta, S.D., Wilcox, T. & Lester, B.M. (2011). Prenatal methamphetamine

exposure and neonatal neurobehavioral outcome in the USA and New Zealand. *Neurotoxicology and Teratology*, 33(1):166–75.

Landgren, M., Svensson, L., Strömland, K. & Andersson Grönlund, M. (2010). Prenatal alcohol exposure and neurodevelopmental disorders in children adopted from Eastern Europe. *Pediatrics*, 125(5):e1178–85.

Lester, B.M., Bagner, D.M., Liu, J., LaGasse, L.L., Seifer, R., Bauer, C.R., Shankaran, S., Bada, H., Higgins, R.D. & Das, A. (2009). Infant neurobehavioral dysregulation: behavior problems in children with prenatal substance exposure. *Pediatrics*, 124(5):e1355–62.

Lester, B.M. & Lagasse, L.L. (2010). Children of addicted women. *Journal of Addictive Diseases*, 29(2):259–76.

London, L. (1999). The 'dop' system, alcohol abuse and social control amongst farm workers in South Africa: a public health challenge. *Social Science & Medicine*, 48(10):1407–14.

London, L., Sanders, D. & Te Water Naude, J. (1998). Farm workers in South Africa – the challenge of eradicating alcohol abuse and the legacy of the 'dop' system. *South African Medical Journal*, 88:1092–95.

Lu, L.H., Johnson, A., O'Hare, E.D., Bookheimer, S.Y., Smith, L.M., O'Connor, M.J., Sowell, E.R. (2009).Effects of prenatal methamphetamine exposure on verbal memory revealed with functional magnetic resonance imaging. *Journal of Developmental and Behavioral Pediatrics*, 30(3):185–92.

May, P.A., Fiorentino, D., Gossage, J., Kalberg, W.O., Hoyme, E.H., Robinson, L.K., Coriale, G., Jones, K.L, Del Campo, M., Tarani, L., Romeo, M., Kodituwakku, P.W., Deiana, L., Buckley, D. & Ceccanti, M. (2006). Epidemiology of FASD in a province in Italy: Prevalence and characteristics of children in a random sample of schools. *Alcoholism: Clinical & Experimental Research*, 30(9):1562–75.

May, P.A., Gossage, J.P., Brooke, L.E., Snell, C.L., Marais, A.S., Hendricks, L.S., Croxford, J.A. & Viljoen, D.L. (2005). Maternal risk factors for fetal alcohol syndrome in the Western Cape province of South Africa: a population-based study. *American Journal of Public Health*, 95(7):1190–99.

May, P.A., Gossage, J.P., Marais, A.S., Adnams, C.M., Hoyme, H.E., Jones, K.L., Robinson, L.K., Khaole, N.C., Snell, C., Kalberg, W.O., Hendricks, L., Brooke, L., Stellavato, C. & Viljoen D.L. (2007). The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. *Drug and Alcohol Dependence*, 88(2–3):259–71.

May, P.A., Brooke, L., Gossage, J.P., Croxford, J., Adnams, C.M., Jones, K.L., Robinson, L. & Viljoen D. (2000). Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *American Journal of Public Health*, 90(12):1905–12.

May, P.A., Gossage, J.P., White-Country, M., Goodhart, K., Decoteau, S., Trujillo, P.M., Kalberg, W.O., Viljoen, D.L. & Hoyme, H.E. (2004). Alcohol consumption and other maternal risk factors for fetal alcohol syndrome among three distinct samples of women before, during, and after pregnancy: the risk is relative. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, 127C(1):10–20.

Meintjes, E.M., Jacobson, J.L., Molteno, C.D., Gatenby, J.C., Warton, C., Cannistraci, C.J., Hoyme, H.E., Robinson, L.K., Khaole, N., Gore, J.C. & Jacobson, S.W. (2010). An FMRI study of number processing in children with fetal alcohol syndrome. *Alcoholism: Clinical & Experimental Research*, 34(8):1450–64.

Nguyen, D., Smith, L.M., Lagasse, L.L., Derauf, C., Grant, P., Shah, R., Arria, A., Huestis, M.A., Haning, W., Strauss, A., Della Grotta, S., Liu, J. & Lester, B.M. (2010). Intrauterine growth of infants exposed to prenatal methamphetamine: results from the infant development, environment, and lifestyle study. *Journal of Pediatrics*, 157(2):337–39.

Oberlander, T.F., Jacobson, S.W., Weinberg, J., Grunau, R.E., Molteno, C.D. & Jacobson, J.L. (2010). Prenatal alcohol exposure alters biobehavioral reactivity to pain in newborns. *Alcoholism: Clinical & Experimental Research*, 34(4):681–92.

O'Callaghan, F.V., Al Mamun, A., O'Callaghan, M., Alati, R., Williams, G.M. & Najman, J.M. (2010). Is smoking in pregnancy an independent predictor of academic difficulties at 14 years of age? A birth cohort study. *Early Human Development*, 86(2):71–76.

O'Connor, M.J., Kogan, N. & Findlay, R. (2002). Prenatal alcohol exposure and attachment behaviour in children. *Alcoholism: Clinical & Experimental Research*, 26(10):1593–602.

O'Connor, M.J. & Paley, B. (2006). The relationship of prenatal alcohol exposure and the postnatal environment to child depressive symptoms. *Journal of Pediatric Psychology*, 31(1):50–64.

O'Connor, M.J. & Paley, B. (2009). Psychiatric conditions associated with prenatal alcohol exposure. *Developmental Disabilities Research Reviews*, 15(3):225–34.

O'Hare E.D., Lu, L.H., Houston, S.M., Bookheimer, S.Y., Mattson, S.N., O'Connor, M.J. & Sowell, E.R. (2009). Altered frontal-parietal functioning during verbal working memory in children and adolescents with heavy prenatal alcohol exposure. *Human Brain Mapping*, 30(10):3200–208.

Olds, D. (1997). Tobacco exposure and impaired development: a review of the evidence. *MRDD Research Reviews*, 3(3):257–69.

Peadon, E., Rhys-Jones, B., Bower, C. & Elliott, E.J. (2009). Systematic review of interventions for children with Fetal Alcohol Spectrum Disorders. *BMC Pediatrics*, 25(9):35.

Premji, S., Benzies, K., Serrett, K. & Hayden, K.A. (2007). Research-based interventions for children and youth with a Fetal Alcohol Spectrum Disorder: revealing the gap. *Child: Care, Health and Development*, 33(4):389–97

Randall-Mkosi, K., London, L., Adnams, C.M., Morojele, N., McLoughlin, J.-A. & Goldstone, C. (2008). *Fetal Alcohol Spectrum Disorder in South Africa: Situational and Gap Analysis*. UNICEF South Africa Report. Available from: www.unicef.org/southafrica/SAF_resources_fas.pdf; accessed 13 July 2011.

Richardson, G.A., Ryan, C., Willford, J., Day, N.L. & Goldschmidt, L. (2002). Prenatal alcohol and marijuana exposure: effects on neuropsychological outcomes at 10 years. *Neurotoxicology and Teratology*, 24(3):309–20.

Riley, E.P., Mattson, S.N., Li, T.K., Jacobson, S.W., Coles, C.D., Kodituwakku, P.W., Adnams, C.M. & Korkman, M.I. (2003). Neurobehavioral consequences of prenatal alcohol exposure: an international perspective. *Alcoholism: Clinical & Experimental Research*, 27(2):362–73.

Riley, E.P. & McGee, C.L. (2005). Fetal alcohol spectrum disorders: an overview with emphasis on changes in brain and behavior. *Experimental Biology and Medicine (Maywood)*, 230(6):357–65.

Roza, S.J., Verhulst, F.C., Jaddoe, V.W., Steegers, E.A., Mackenbach, J.P., Hofman, A. & Tiemeier, H. (2009). Maternal smoking during pregnancy and child behaviour problems: the Generation R Study. *International Journal of Epidemiology*, 38(3):680–89.

Sampson, P.D., Streissguth, A.P., Bookstein, F.L., Little, R.E., Clarren, S.K., Dehaene, P., Hanson, J.W. & Graham, J.M., Jr. (1997). Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. *Teratology*, 56(5): 317–26.

Sayal, K., Heron, J., Golding, J., Alati, R., Smith, G.D., Gray, R. & Emond, A. (2009). Binge pattern of alcohol consumption during pregnancy and childhood mental health outcomes: longitudinal population-based study. *Pediatrics*, 123(2):e289–96.

Schneider, M., Norman, R., Parry, C., Bradshaw, D. & Plüddemann, A. (2007). Estimating the burden of disease attributable to alcohol use in South Africa in 2000. *South African Medical Journal*, 97:664–72.

Smith, L., Yonekura, M.L., Wallace, T., Berman, N., Kuo, J. & Berkowitz, C. (2003). Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants born at term. *Journal of Developmental and Behavioral Pediatrics*, 24(1):17–23.

Sowell, E.R., Johnson, A., Kan, E., Lu, L.H., Van Horn, J.D., Toga, A.W., O'Connor, M.J. & Bookheimer, S.Y. (2008). Mapping white matter integrity and neurobehavioral correlates in children with fetal alcohol spectrum disorders. *The Journal of Neuroscience*, 28(6):1313–19.

Sowell, E.R., Leow, A.D., Bookheimer, S.Y., Smith, L.M., O'Connor, M.J., Kan, E., Rosso, C., Houston, S., Dinov, I.D. & Thompson, P.M. (2010). Differentiating prenatal exposure to methamphetamine and alcohol versus alcohol and not methamphetamine using tensor-based brain morphometry and discriminant analysis. *The Journal of Neuroscience*, 30(11):3876–85.

Sowell, E.R., Thompson, P.M., Mattson, S.N., Tessner, K.D., Jernigan, T.L., Riley, E.P. & Toga A.W. (2002b). Regional brain shape abnormalities persist into adolescence after heavy prenatal alcohol exposure. *Cerebral Cortex*, 12(8):856–65.

Sowell, E.R., Thompson, P.M., Peterson, B.S., Mattson, S.N., Welcome, S.E., Henkenius, A.L., Riley, E.P., Jernigan, T.L. & Toga, A.W. (2002a). Mapping cortical gray matter asymmetry patterns in adolescents with heavy prenatal alcohol exposure. *NeuroImage*, 17(4):1807–19.

Spadoni, A.D., McGee, C.L., Fryer, S.L. & Riley, E.P. (2007). Neuroimaging and fetal alcohol spectrum disorders. *Neuroscience & Biobehavioral Reviews*, 31(2):239–45.

Streissguth, A.P. & O'Malley, K. (2000). Neuropsychiatric implications and long-term consequences of fetal alcohol spectrum disorders. *Seminars in Clinical Neuropsychiatry*, 5(3):177–90.

Urban, M., Cherisch, M.F., Fourie, L.-A., Chetty, C., Olivier, L., Rosenthal, J. & Viljoen, D. (2008). Fetal alcohol syndrome among grade-one children in the Northern Cape Province: prevalence and risk factors. *South African Medical Journal*, 98(11):877–82.

Viljoen, D.L., Carr, L.G., Foroud, T.M., Brooke, L., Ramsay, M. & Li, T.K. (2001). Alcohol dehydrogenase-2*2 allele is associated with decreased prevalence of fetal alcohol syndrome in the mixed-ancestry population of the Western Cape Province, South Africa. *Alcoholism: Clinical & Experimental Research*, 25(12):1719–22.

Viljoen, D., Croxford, J., Gossage, J.P., Kodituwakku, P.W. & May, P.A. (2002). Characteristics of mothers of children with fetal alcohol syndrome in the Western Cape Province of South Africa: a case control study. *Journal of Studies on Alcohol*, 63(1):6–17.

Viljoen, D. & Craig, P. (2003). Fetal alcohol syndrome – South Africa, 2001. *Morbidity and Mortality Weekly Report*, 52(28):660–62.

Viljoen, D.L., Gossage, J.P., Brooke, L., Adnams, C.M., Jones, K.L., Robinson, L.K., Hoyme, H.E., Snell, C., Khaole, N.C., Kodituwakku, P., Asante, K.O., Findlay, R., Quinton, B., Marais, A.S., Kalberg, W.O., May & P.A. (2005). Fetal alcohol syndrome epidemiology in a South African community: a second study of a very high prevalence area. *Journal of Studies on Alcohol*, 66(5):593–604.

Willford, J.A., Chandler, L.S., Goldschmidt, L. & Day, N.L. (2010). Effects of prenatal tobacco, alcohol and marijuana exposure on processing speed, visual-motor coordination, and interhemispheric transfer. *Neurotoxicology and Teratology*, 32(6):580–88.

Williams, G.M., O'Callaghan, M., Najman, J.M., Bor, W., Andersen, M.J. & Richards, D.U.C. (1998). Maternal cigarette smoking and child psychiatric morbidity: a longitudinal study. *Pediatrics*, 102(1):e11.

4 Women and alcohol

Bronwyn Myers and Bavanisha Vythilingum

Introduction

Female drinkers who consume alcohol at risky levels seem more vulnerable to the adverse consequences of problem drinking than do their male counterparts. For instance, there is compelling evidence that women progress faster to problem drinking and alcohol dependence than men, and compared to men experience an earlier onset (or telescoping) of alcohol-related complications (Ashley et al, 1977). Also, female drinkers report more severe alcohol-related psychiatric, medical and social problems relative to their male counterparts. This telescoping is also evident in drug-dependent women (Hernandez-Avila et al, 2004).

Prevalence of alcohol use among South African women

Although a relatively low proportion of South African women report ever drinking alcohol (22%), those women who do drink often report drinking at harmful (two to four drinks per day for women) or hazardous levels (four or more drinks per day for women) (Parry et al). Furthermore, despite findings that a much higher proportion of South African men report the lifetime consumption of alcohol relative to women, both the 1998 and 2003 South African Demographic and Health Surveys (SADHS) found that levels of problematic alcohol use among women are not substantially different from those of men (Parry et al, 2005; Department of Health, 2007). For example, the 2003 SADHS found that 12% of male and 14% of female drinkers reported consuming alcohol at hazardous or harmful levels in the 12 months preceding the survey (Department of Health, 2007). Similarly, the first National Youth Risk Behaviour Survey found that although higher proportions (38.5%) of male learners than female learners (26.4%) were current drinkers, of these current drinkers, similar proportions of male and females reported episodic binge drinking in the month preceding the study (Morojele et al, 2002). In South Africa, hazardous and harmful drinking appears to be especially high over weekends, with 23% of male and 25% of female drinkers in the 2003 SADHS exceeding the World Health Organization and South African National Department of Health recommended levels for responsible drinking (Department of Health, 2007).

The 2003 SADHS also found that 6.9% of women self-reported symptoms of alcohol abuse or dependence, as measured by a score of two or greater on the CAGE questionnaire (Department of Health, 2007). Given the limitations of omnibus surveys, such as the SADHS (which lack the detailed and repetitive questioning needed to obtain more accurate estimates of use), these proportions are likely to be underestimates of alcohol use and associated problems among women. South African women are quite likely to under-report their use of alcohol due to the stigma surrounding women's use of alcohol (Myers

et al, 2009) and cultural norms that sanction women's drinking in many South African communities.

South African women tend to have higher rates of problem drinking compared to their counterparts worldwide. Although prevalence rates vary widely by country, worldwide rates range from 0.2% to 3.9%, with only the United States (6.4%) approaching rates cited for South African women (Somers et al, 2004). South Africa is also unusual in that women and men have a similar prevalence of alcohol use disorders; internationally, alcohol use disorders are two to five times more common in men than women (Somers et al, 2004).

Of course, a proxy indicator for the prevalence of alcohol misuse among South African women stems from findings about the high prevalence of fetal alcohol spectrum disorders (FASD) in South Africa. The epidemiology of FASD is thoroughly examined in Chapter 3 of this book.

Data from the South African Community Epidemiology Network on Drug Use (SACENDU) Project also highlight the prevalence of alcohol-related problems among South African women. Over time, and across all regions of the country, alcohol remains one of the most frequently reported primary substances of abuse among women attending substance abuse treatment services in the country (Plüddemann et al, 2009).

Irrespective of the methodological challenges associated with estimating the prevalence of alcohol use disorders among South African women, taken together these findings point to problematic patterns of alcohol consumption among women in the country. For women, patterns of episodic binge drinking and heavy alcohol consumption are concerning, given the negative clinical and behavioural consequences associated with women's heavy use of alcohol. Some of these key consequences are discussed in the following section.

Clinical and behavioural consequences of alcohol use among women

Compared to men, women who abuse alcohol appear to have a higher level of medical difficulties, and higher mortality. Part of this may be due to so-called telescoping of sequelae, where women seem to develop problems after less exposure to alcohol than men. Ashley et al (1977) found that although alcoholic men began drinking and misusing alcohol at earlier ages than women, rates of most alcohol-related disease entities were similar between alcoholic men and women, and women contracted these illnesses after significantly less consumption of alcohol. Holman et al (1996) performed meta-analyses of cohort and epidemiological studies and found that, despite lower reported consumption of alcohol, women have higher all-cause mortality related to alcohol use. This may be due to differences in pharmacokinetics between men and women – women develop higher alcohol concentrations for the same amount of ingested alcohol.

The pattern of sequelae also differs: in women, excess mortality risk appears to result from cirrhosis, cancer and injury, as opposed to cardiovascular risks as seen in men (Klatsky et al, 1992; Fuchs et al, 1995). Women, by virtue of their gender, also have some unique vulnerabilities, namely, pregnancy and menstrual-related problems. The classic pregnancy-related sequelae of alcohol consumption are the fetal alcohol spectrum disorders. These are discussed in detail in Chapter 3.

Liver disease

There is consistent evidence that women experience accelerated courses of liver disease at levels of alcohol consumption tolerated by men. Several UK studies have reported women to be more susceptible to cirrhosis after less alcohol consumption, and that women tend to have more advanced disease at presentation (Morgan & Sherlock, 1977; Levi & Chalmers, 1978; Saunders et al, 1981). Furthermore, in a 12-year prospective study in Copenhagen (N = 13285; 7234 women), Becker et al (1996) reported a steeper dose-response curve between alcohol use and liver disease for women than for men.

Cancer

Alcohol use appears to play a role in increasing risk for all cancers, and specifically for cancer of the reproductive system. In South African women, alcohol use has been associated with an increased risk of breast cancer (Schneider et al, 2000). This is possibly due to alcohol's effect of raising estradiol levels, and may account for the finding of increased risk for breast cancer associated with the concomitant use of alcohol and hormone replacement therapy (Zumoff, 1997). Similarly, an association between alcohol consumption and post-menopausal endometrial cancer has been found (Gapstur et al, 1994).

Endocrine and gynaecologic disorders

Alcohol abuse in women is associated with alterations of the menstrual cycle and impaired fertility. Gavaler and colleagues (Gavaler et al, 1983) presented evidence that alcohol abuse is associated with an increased prevalence of amenorrhoea (independent of cirrhosis). Furthermore, alcohol-related exacerbations of severe premenstrual symptoms have been described (Ehlers et al, 1996; Lammers et al, 1995). Wilsnack et al (1984) reported an association between high levels of alcohol use and rates of gynaecologic surgery (other than hysterectomy), infertility and stillbirth. This may be due to different responses of central neurosteroid mechanisms to alcohol in women. Animal models suggest alterations in GABA responses and production/modulation of neurosteroids in females as compared to males; however, this is yet to be confirmed in humans (Lancaster, 1994).

Psychiatric disorders

The National Epidemiological Study on Alcohol and Related Conditions (NESARC) (Compton et al, 2007) was a large US population-based study that examined 12-month and lifetime prevalence of drug abuse and dependence and the associated correlates, treatment rates, disability and comorbidity with other Axis I and II disorders. It found significantly higher lifetime comorbidity of psychiatric disorders in alcoholic women as compared to men (72% vs 52%), despite similar prevalence rates of alcohol dependence. Women reported significantly more anxiety disorders (social phobia, simple phobia and PTSD), mood disorders (depression, mania) and drug dependence (tranquillisers) than men. Women also exhibited more multiple comorbidity, ie, two or more psychiatric disorders in addition to alcohol dependence (32% women vs 14 % men). Similar findings were reported in the Baltimore Epidemiological Catchment area study (ECA) (Regier et al, 1990), as well as in studies of subjects seeking treatment for alcohol dependence (Schuckit et al, 2001).

The pattern of onset of psychiatric disorders also differs between men and women. Women are more likely to have a primary mood/anxiety disorder predating the onset of alcohol abuse (Schuckit et al, 1998; Compton et al, 2007), whereas men usually develop these disorders as a consequence of alcohol abuse. Hence psychiatric comorbidity is more of a risk factor for the development of an alcohol or drug use disorder in women than men (Schuckit et al, 1998). Furthermore, in women with comorbid depression and alcohol abuse who present for treatment, depressive symptoms tend to be worse than symptoms of alcohol use disorders, whereas women with alcohol abuse only, have similar severity of alcohol symptoms as do men.

Alcohol and comorbid Axis I disorders present a potent combination for increased suicide risk. Women with combined Axis 1 and alcohol use disorders show between 1.7 and 2.2 times more suicidal ideation and suicide attempts than men (Compton et al, 2007). These findings have important treatment implications: in men, comorbid psychiatric disorders are likely to resolve with treatment of the alcohol disorder, whereas for women direct treatment of the psychiatric disorder is usually required.

Cognition also appears to be differentially affected by alcohol abuse. Women alcoholics have been reported to perform poorly, compared to their male counterparts, on tests of spatial memory (Acker, 1986), constructive thinking (Giancola, 2000) and attention (Glenn et al, 1993; Nixon et al, 1995). However, these results are difficult to interpret because of comorbidity confounds – for example, higher rates of depression, anxiety and hostility (all of which impact on cognitive functioning) have been found among heavily drinking women (Nixon et al, 1995; Robinson et al, 2000).

Neuroimaging studies have found structural differences in the brains of men and women. Two studies using computerised tomography to measure cerebrospinal fluid (CSF) have compared the brain structure of male and female alcoholics (Hommer et al, 2001). Both reported that men and women with alcohol dependence show similarly greater intracranial CSF than control subjects, despite a shorter duration of excessive drinking and a smaller average daily alcohol consumption among the women. Direct comparisons of men and women with alcohol dependence showed that the proportion of intracranial contents occupied by grey matter was smaller in women than in men. The magnitudes of differences in brain volumes adjusted for intracranial size between women with alcohol dependence and women without alcohol dependence were greater than the magnitude of the adjusted differences between men with alcohol dependence and men without alcohol dependence. These results are consistent with greater sensitivity to alcohol neurotoxicity among women.

Sexual risk behaviour and HIV transmission

Another major consequence of alcohol and other drug (AOD) use among women relates to its role as a determinant of sexual risk behaviour and its contribution to HIV transmission in South Africa (Morojele et al, 2006; Rehm & Parry, 2009). AOD use is associated with disinhibition and impaired judgment that may lead to sexual risk behaviours such as inconsistent condom use (Morojele et al, 2006; Rawson et al, 2008; Strathdee & Sherman, 2003). In South Africa, this is especially worrisome, given that women are already more at risk for HIV due to their

biological vulnerability and the high levels of sexual victimisation in the country (Dunkle et al, 2005). In addition, various South African studies report significant associations between gender, substance use, sexual risk behaviour and risk for victimisation (see, for example, Kalichman et al, 2007; Wechsberg et al, 2005). Substance use prevents women from identifying potential situations that place them at risk for sexual victimisation (Wechsberg et al, 2005). This is particularly important, as in many South African communities women who use drugs are viewed as sexually available, which increases their chances of being victimised or coerced into sex (Myers et al, 2009; Sawyer et al, 2006). Also, many female drug users may exchange sex for drugs or money to buy drugs (Sawyer et al, 2006). In both of these instances, women's ability to negotiate condom use and safe sex practices is reduced.

Taken together, these findings highlight the importance of developing and implementing preventive and early intervention that address the intersection between AOD use, infectious disease risk and risk of victimisation for women. There is extensive evidence that, in the absence of dependence, early intervention (comprising early identification of risky drinking and the provision of brief advice for people who drink at hazardous or harmful levels) is effective in reducing risky patterns of alcohol use and preventing the behavioural and clinical consequences associated with problematic substance use (WHO, 2009). Apart from interventions that focus solely on reducing alcohol (and other drug) consumption, there is a clear need for interventions that target AOD use, infectious disease and victimisation risk in an integrated manner.

In South Africa, several randomised controlled trials of integrated HIV and violence risk reduction interventions for substance-using women have been tested. For example, the Women's Health CoOp intervention, an evidence-based intervention developed in the United States, has been adapted for the South African context. This brief community-based intervention focuses on: (1) empowering women to change their substance use behaviour and thereby reduce their substance-related sexual risks, and (2) equipping women with condom use, relationship negotiation and conflict resolution skills to enable them to practise safer sex and reduce their risk of victimisation (Wechsberg et al, 2009). In South Africa, various studies found that women assigned to this intervention showed significantly greater reductions in their AOD intake and their sexual risk behaviours, and reported being victimised less often than women assigned to the control condition (Wechsberg et al, 2006; Wechsberg et al, 2008). In addition, this intervention appears equally effective in individual and group formats (Wechsberg et al, 2006) and for women from different ethnic groups and regions of the country (Sawyer et al, 2006; Wechsberg et al, 2006; Wechsberg et al, 2008). These community studies show that interventions targeting the intersection between substance use and other risk behaviours are effective for preventing the negative consequences associated with women's substance use. However, for these research-based interventions to have any real effect on South African women's risk behaviours they need to be adopted by health and social welfare agencies working with high-risk women and implemented on a much broader scale. This would require providing agency workers, who may not form part of the traditional substance abuse workforce, with education and training on brief interventions for substance use and the ways in which substance use augments women's risks for HIV and victimisation.

Substance abuse services for women in South Africa

Given the high prevalence of problem drinking among South African female drinkers and the clinical and behavioural consequences associated with substance use among women, it is essential for women to have access to a broad range of substance-related prevention, early intervention and treatment services. Prevention and early intervention services suitable for use among women (including services for the prevention of FASD) have been described in other chapters, so this section will focus on describing the availability and appropriateness of substance abuse treatment services for South African women.

Availability of, and access to, substance abuse treatment for South African women

A convergence of evidence suggests that women with substance use disorders are less likely, over their lifetime, to enter treatment than their male counterparts (Greenfield et al, 2007a; Sun et al, 2006; Luseno et al, 2010). South African research findings also suggest that women are underrepresented in substance abuse treatment facilities. For example, in several regions of the country women comprised less than a fifth of the total treatment population for the second half of 2008 (see Table 4.1) (Plüddemann et al, 2009).

Women from disadvantaged South African communities are especially underrepresented in substance abuse treatment services, accounting for only a small proportion of the total population of women in treatment. For example, private for-profit treatment facilities serve the largest proportion of female clients, who comprise primarily white South Africans with the financial means to pay for treatment (Myers et al, 2009; Myers & Fakier, 2007). Taken together, these findings probably reflect the limited extent to which poor women specifically (and women in general) are able to access substance abuse treatment services in South Africa rather than lower levels of treatment need among substance-using women.

Table 4.1: Proportion of women admitted to substance abuse treatment, by province (January–June 2008)*

Region/province	Proportion of women in treatment (%)	Proportion of women <20 years old in treatment (%)
Gauteng	18	13
KwaZulu-Natal	11	–
Eastern Cape	20	16
Northern Region#	11	13
Free State	17	4
North West	24	5
Northern Cape	19	15
Western Cape	25	22

* Extracted from the South African Community Epidemiology Network on Drug Use Project (Parry et al)
\# Northern Region refers to Limpopo and Mpumalanga provinces.

Evidence that women from disadvantaged South African communities experience more barriers to accessing treatment services than their male counterparts provides partial support for this explanation (Myers & Fakier, 2007). In addition, even though the most powerful barriers to substance abuse treatment utilisation for women are similar to those experienced by men (limited awareness of when, where and how to access services; geographic access barriers, such as lengthy travel times; affordability barriers, including competing financial priorities; and concerns about treatment), these barriers disproportionately affect women's use of treatment services relative to their male counterparts (Myers, 2007). The saliency of these barriers for poor women relative to men is partly attributable to the patriarchal nature of South African society, where the incomes of many poor South African women are controlled by their male partners; women therefore are less likely than men to be able to afford the direct or indirect (travel) costs associated with treatment. In addition, many poor households in South Africa remain female-headed, where there is a constant struggle for survival (Coovadia, 2009). For women in these households, accessing treatment is less of a priority than ensuring that the basic needs of their families are met.

These findings highlight the importance of improving the availability and affordability of substance abuse treatment services for poor women in the country. Outpatient mobile clinics are an affordable way of improving service availability while ensuring that new services are located within communities and are therefore geographically accessible. The costs associated with commuting to treatment can also be reduced by providing women with tokens for public transport.

Apart from difficulties in accessing available substance abuse services, another challenge to women's uptake of, and engagement in, substance abuse treatment is their concern about the quality and gender-appropriateness of care (Myers et al, 2009). For women, an important indicator of service appropriateness is the degree to which services are gender-responsive.

Towards gender-responsive substance abuse treatment services: gaps in the appropriateness of care

Although the evidence-based practice guidelines described in Chapter 2 apply to the treatment of women, female substance users often have more complex and varied treatment needs than their male counterparts, and may therefore require more comprehensive and intensive services (Greenfield et al, 2007a.). There is compelling evidence that, when compared to men, women are likely to have more severe AOD problems on treatment entry (Arfken et al, 2001; Simpson & McNulty, 2008), more severe and greater co-occurring mental disorders (De Wilde et al, 2004; Grella & Greenwell, 2007; Langan & Pelissier, 2001), multiple traumas related to childhood physical and sexual abuse (Farley, 2004; Grella & Greenwell, 2007; Sacks et al, 2008; Stewart et al, 1996), greater problems related to intimate partner violence (Chermack et al, 2000; Fals-Stewart & Kennedy, 2005) and more unstable housing environments (Grella & Greenwell, 2007; Simpson & McNulty, 2008; Wenzel et al, 2001).

These findings have important implications for the delivery of treatment services. First, women in substance abuse treatment appear to have very different treatment needs

compared to their male counterparts (Grella & Greenwell 2007; Simpson & McNulty, 2008). Effective treatment for women thus requires that treatment programmes tailor their services to meet the unique needs of female clients. Such tailoring would involve assessing the problem-severity and service needs of all female clients on multiple domains of functioning (including mental health, family and parenting, health and vocational or occupational domains) and providing female clients with a comprehensive menu of service options targeted at meeting their specific set of needs (Grella & Greenwell, 2007; Sacks et al, 2008; Simpson & McNulty, 2008; Sun et al, 2006). The importance of providing female clients with a comprehensive range of services is highlighted by findings from a large US study on treatment effectiveness. This prospective cohort study of 3 142 clients (1 123 women and 2 019 men) from 59 treatment facilities found that, although both men and women benefit from the provision of comprehensive services, the impact of these services on post-treatment substance use outcomes is greater for women relative to men, even when individual pre-treatment characteristics are controlled for (Marsh et al, 2004).

Access to gender-responsive mental health services is particularly important for female substance use outcomes. Studies comparing the substance use outcomes of women assigned to treatment programmes that offer integrated, gender-responsive mental health and trauma services to the outcomes of women assigned to treatment-as-usual report better outcomes for women assigned to the integrated service conditions (Clark & Power, 2005; Messina et al, 2009). For example, a randomised trial of a gender-responsive substance abuse treatment programme for female prisoners (which addressed women-specific treatment needs related to trauma) found that women randomised to this condition had greater reductions in drug use, were more likely to remain in continuing care services, and were less likely to be reincarcerated than women randomised to a standard treatment programme with no focus on women-specific issues (Messina et al, 2009). Despite persuasive evidence that the provision of comprehensive, integrated substance abuse and mental health services improves women's treatment outcomes, access to mental health and other wrap-around health and social welfare services is limited in South African treatment. Findings from audits of treatment services in the country show that less than a quarter of services provide clients with access to mental health services (Myers et al, 2007). This raises concerns about the effectiveness of current treatment services for women with substance use disorders, who often have high levels of co-occurring mental disorders (Sun et al, 2006).

Another gender-responsive service consistently associated with better treatment outcomes for women is the provision of childcare services within the course of treatment (Claus et al, 2007). The provision of these services addresses a major barrier to women's entry into, and engagement in, substance abuse treatment (Appel et al, 2004; Myers, 2007; Stewart et al, 2007; Tucker et al, 2004), thereby improving treatment outcomes. For instance, one large national study of outpatient treatment services in the United States found a significant positive relationship between the provision of childcare services and length of stay in treatment for female clients, with treatment duration being a powerful predictor of improved substance use outcomes (Claus et al, 2007). In addition, a systematic review of 35 empirical studies that included solely women subjects, or that analysed female subjects separately from male subjects, revealed that the provision of childcare services was a key component of effective substance abuse treatment for women (Sun et al, 2006). Despite this, audits of

substance abuse treatment facilities in seven of the nine South African provinces reveal that few treatment services are providing gender-responsive services aimed at addressing the unique service needs of their female population, with only around a third of these facilities providing any form of childcare service (Fakier & Myers, 2008; Myers & Fakier, 2007). This raises questions about whether existing substance abuse treatment services are able to meet the service needs of their female population.

Given the multiple and unique treatment needs of women with substance use disorders, several researchers have suggested that gender-specific or women-only services may be more effective for the treatment of substance use disorders than mixed-gender programmes (Sun et al, 2006). This is mainly because women form a minority group in treatment facilities and may feel uncomfortable talking about traumatic or abusive experiences related to their substance use in front of male participants (Greenfield et al, 2007a). Yet a systematic review of studies examining the effectiveness of gender-specific programmes found that women-specific treatment services are only more effective than mixed-gender programmes when they provide comprehensive services to address the range of problems more common to substance-using women or special subgroups of this population, such as pregnant women (Greenfield et al, 2007b). For gender-specific services to attain their potential, they therefore need to provide a broad range of comprehensive mental health and medical services, life skills (including vocational and parenting training) and social services (such as child care) to women who may need them (Uziel-Miller & Lyons, 2000).

Apart from short-term treatment gains, women receiving comprehensive gender-specific services also show sustained or continued improvement in their treatment outcomes compared to women who receive mixed-gender services (Greenfield et al, 2007b; Niv & Hser, 2007; Sun et al, 2006). For example, a prospective longitudinal study found women treated in comprehensive women-only substance abuse treatment programmes had better substance use outcomes at follow-up than those treated in mixed-gender programmes, despite higher levels of initial problem severity among women in the women-only programmes (Niv & Hser, 2007). In addition, a randomised controlled trial found that participants within the gender-specific treatment condition had significantly greater reductions in drug and alcohol use over the six-month post-treatment follow-up phase compared to participants in the mixed-gender group (Greenfield et al, 2007a). Another large quasi-experimental study found that women admitted to agencies providing specialised women-only treatment were significantly more likely to complete treatment and engage in continuing care services (two markers for sustained treatment gains) than women admitted to standard mixed-gender treatment services (Claus et al, 2007).

Despite this convincing body of evidence, South Africa has few gender-specific treatment services. For example, a recent audit of treatment facilities in the country found that only 6% of treatment facilities in the central and northern regions of the country (together comprising the Free State, North West, Northern Cape, Limpopo and Mpumalanga provinces) reported providing women-only treatment services (Fakier & Myers, 2008). While the proportion of facilities providing women-only services is somewhat higher in other parts of the country, it still remains low, at less than a quarter of services (Myers & Fakier, 2007). In addition, there are no treatment services presently available in the country that are oriented towards the specific needs of pregnant, substance-dependent women, although many facilities do accept

pregnant women into their mixed-gender programmes. These findings raise concerns about the appropriateness and quality of services available to women with substance use disorders in the country and highlight the urgent need to expand services to include women-only treatment streams that provide comprehensive services tailored to meet the multiple needs of women with substance use disorders. Treatment programmes for pregnant women also need to be introduced. For these new services to be effective, service providers will require extensive training on evidence-based treatment approaches for women and ways of appropriately managing women-specific service needs (such as interpersonal violence, trauma, parenting and pregnancy-related issues). These efforts will also require greater cooperation between the Departments of Health (responsible for the delivery of health and mental health services) and Social Development (responsible for the delivery of substance abuse services) to ensure that women in substance abuse treatment receive prioritised mental health and other wrap-around health services (including antenatal care) during the course of substance abuse treatment.

Conclusion

In South Africa, people who consume alcohol tend to do so in a risky manner, and relatively similar proportions of men and women drink at risky levels (Parry et al, 2005). This is cause for concern, as women are more vulnerable to the negative consequences of risky drinking (and other drug use). Some of the major behavioural consequences of risky drinking and other drug use for South African women are increased risk of victimisation (such as through sexual coercion or interpersonal violence) and increased HIV-related sexual risks. From this discussion, it is apparent that there is a clear need to implement early intervention programmes which target these intersecting HIV and victimisation risks for women who use substances problematically but are not substance-dependent. Effective research-based programmes need to be adopted by state and private partners to facilitate broad implementation and ensure sustained benefits.

As early interventions are not intensive enough to change substance use behaviour among women who are already substance-dependent, it is important to ensure that women with these disorders are able to access substance abuse treatment services. It is quite evident that women remain under-represented in substance abuse treatment services, especially poor women from the rural provinces of the country. To improve the use of treatment services by women, affordability and geographic access barriers to treatment utilisation need to be addressed. Apart from this, there are concerns about the appropriateness of current services and the extent to which they are able to meet the unique service needs of female clients. To address these concerns, services need to improve the extent to which they offer comprehensive services that are responsive to women's treatment needs. These gender-responsive services may include the provision of mental health services that address trauma, gender-based violence and other mental health issues that often co-occur alongside female substance use, and the provision of childcare services that allow women to remain engaged in treatment. The availability of women-only treatment programmes (or services within mixed-gender facilities) also needs to be improved.

It is clear that a large amount of work needs to be done to improve access to, and the quality of, substance abuse services for women in South Africa. This may require mainstreaming interventions for women with substance use disorders into the public health system where vulnerable women are typically served (such as reproductive health, children's health and HIV services within community clinics). For instance, all women of child-bearing age attending primary healthcare services should be routinely screened for alcohol (and other drug) use. Preconception screening is especially important to prevent alcohol-exposed (or other drug-exposed) pregnancies. Those women who are identified as being at risk for a substance-exposed pregnancy would then benefit from an early intervention programme to stop or reduce drinking and/or increase their use of contraception. Such interventions however will require better cooperation between the Departments of Health (responsible for the delivery of primary health services) and Social Development (responsible for the delivery of substance abuse services) and close collaboration between researchers, policy-makers, service planners and service providers in both the public and private health and social welfare service sectors. In addition, any effort to improve services for women needs to be carefully monitored to ensure that service improvements translate into improved substance use outcomes.

References

Acker, C. (1986). Neuropsychological deficits in alcoholics: the relative contributions of gender and drinking history. *British Journal of Addiction,* 81(3):395–403.

Appel, P.W., Ellison, A.A., Jansky, H.K. & Oldak, R. (2004). Barriers to enrollment in drug abuse treatment and suggestions for reducing them: opinions of drug injecting street outreach clients and other system stakeholders. *American Journal of Drug and Alcohol Abuse,* 30(1):129–53.

Arfken, C.L., Klein, C., Di Menza, S. & Schuster, C.R. (2001). Gender differences in problem severity at assessment and treatment retention. *Journal of Substance Abuse Treatment*, 20(1):53–57.

Ashley, M.J., Olin, J.S., Le Riche, W.H., Kornaczewski, A., Schmidt, W. & Rankin, J.G. (1977). Morbidity in alcoholics. Evidence for accelerated development of physical disease in women. *Archives of Internal Medicine*, 137(7):883–87.

Becker, U., Deis, A., Sorensen, T.I., Gronbaek, M., Borch-Johnsen, K., Muller, C.F., Schnohr, P. & Jensen, G. (1996). Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology,* 23(5):1025–29.

Chermack, S.T., Murray, R.L., Walton, M.A., Booth, B.A., Wryobeck, J. & Blow, F.C. (2008). Partner aggression among men and women in substance use disorder treatment: correlates of psychological and physical aggression and injury. *Drug and Alcohol Dependence*, 98(1–2):35–44.

Clark, H.W. & Power, A.K. (2005). Women, Co-occurring Disorders, and Violence Study: a case for trauma-informed care. *Journal of Substance Abuse Treatment*, 28(2):145–46.

Claus, R.E., Orwin, R.G., Kissin, W., Krupski, A., Campbell, K. & Stark, K. (2007). Does gender-specific substance abuse treatment for women promote continuity of care? *Journal of Substance Abuse Treatment*, 32(1):27–39.

Compton, W.M., Thomas, Y.F., Stinson, F.S. & Grant, B.F. (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Archives of General Psychiatry*, 64(5):566–76.

Coovadia, H. (2009). Current issues in prevention of mother-to-child transmission of HIV-1. *Current Opinion in HIV and AIDS*, 4(4):319–24.

De Wilde, J., Soyez, V., Broekaert, E., Rosseel, Y., Kaplan, C. & Larsson, J. (2004). Problem severity profiles of substance abusing women in European Therapeutic Communities: influence of psychiatric problems. *Journal of Substance Abuse Treatment*, 26(4):243–51.

Department of Health. (2007). *South African Demographic and Health Survey*. Pretoria: Department of Health.

Dunkle, K.L., Beksinska, M.E., Rees, V.H., Ballard, R.C., Htun, Y. & Wilson, M.L. (2005). Risk factors for HIV infection among sex workers in Johannesburg, South Africa. *International Journal of STD & AIDS*, 16(3):256–61.

Ehlers, C.L., Phillips, E. & Parry, B.L. (1996). Electrophysiological findings during the menstrual cycle in women with and without late luteal phase dysphoric disorder: relationship to risk for alcoholism? *Biological Psychiatry*, 39(8):720–32.

Fakier, N. & Myers, B. (2008). Audit of substance abuse treatment facilities in Free State, Limpopo, Mpumalanga, North West and Northern Cape (2007–2008). Technical report. South African Medical Research Council.

Fals-Stewart, W. & Kennedy, C. (2005). Addressing intimate partner violence in substance-abuse treatment. *Journal of Substance Abuse Treatment*, 29(1):5–17.

Fuchs, C.S., Stampfer, M.J., Colditz, G.A., Giovannucci, E.L., Manson, J.E., Kawachi, I., Hunter, D.J., Hankinson, S.E., Hennekens, C.H. & Rosner, B. (1995). Alcohol consumption and mortality among women. *New England Journal of Medicine*, 332(19):1245–50.

Gapstur, S.M., Potter, J.D. & Folsom, A.R. (1994). Alcohol consumption and colon and rectal cancer in postmenopausal women. *International Journal of Epidemiology*, 23(1):50–57.

Gavaler, J.S., Urso, T. & Van Thiel, D.H. (1983). Ethanol: its adverse effects upon the hypothalamic-pituitary-gonadal axis. *Substance and Alcohol Actions/Misuse*, 4(2–3):97–110.

Giancola, P.R. (2000). Executive functioning: a conceptual framework for alcohol-related aggression. *Experimental and Clinical Psychopharmacology*, 8(4):576–97.

Glenn, S.W., Errico, A.L., Parsons, O.A., King, A.C. & Nixon, S.J. (1993). The role of antisocial, affective, and childhood behavioral characteristics in alcoholics' neuropsychological performance. *Alcoholism: Clinical & Experimental Research*, 17(1):162–69.

Greenfield, S.F., Brooks, A.J., Gordon, S.M., Green, C.A., Kropp, F., McHugh, R.K., Lincoln, M., Hien, D. & Miele, G.M. (2007a). Substance abuse treatment entry, retention, and outcome in women: a review of the literature. *Drug and Alcohol Dependence*, 86(1):1–21.

Greenfield, S.F., Trucco, E.M., McHugh, R.K., Lincoln, M. & Gallop, R.J. (2007b). The Women's Recovery Group Study: a Stage I trial of women-focused group therapy for substance use disorders versus mixed-gender group drug counseling. *Drug and Alcohol Dependence*, 90(1):39–47.

Grella, C.E. & Greenwell, L. (2007). Treatment needs and completion of community-based aftercare among substance-abusing women offenders. *Women's Health Issues,* 17(4):244–55.

Hernandez-Avila, C.A., Rounsaville, B.J. & Kranzler, H.R. (2004). Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. *Drug and Alcohol Dependence*, 74(3):265–72.

Holman, C.D., English, D.R., Milne, E. & Winter, M.G. (1996). Meta-analysis of alcohol and all-cause mortality: a validation of NHMRC recommendations. *The Medical Journal of Australia*, 164(3):141–45.

Hommer, D., Momenan, R., Kaiser, E. & Rawlings, R. (2001). Evidence for a gender-related effect of alcoholism on brain volumes. *American Journal of Psychiatry*, 158(2):198–204.

Kalichman, S.C., Simbayi, L.C., Jooste, S. & Cain, D. (2007). Frequency, quantity, and contextual use of alcohol among sexually transmitted infection clinic patients in Cape Town, South Africa. *American Journal of Drug and Alcohol Abuse*, 33(5):687–98.

Klatsky, A.L., Armstrong, M.A. & Friedman, G.D. (1992). Alcohol and mortality. *Annals of Internal Medicine*, 117(8):646–54.

Lammers, S.M., Mainzer, D.E. & Breteler, M.H. (1995). Do alcohol pharmacokinetics in women vary due to the menstrual cycle? *Addiction,* 90(1):23–30.

Lancaster, F.E. (1994). Gender differences in the brain: implications for the study of human alcoholism. *Alcoholism: Clinical & Experimental Research*, 18(3):740–46.

Langan, N.P. & Pelissier, B.M. (2001). Gender differences among prisoners in drug treatment. *Journal of Substance Abuse*, 13(3):291–301.

Levi, A.J. & Chalmers, D.M. (1978). Recognition of alcoholic liver disease in a district general hospital. *Gut,* 19(6):521–25.

Luseno, W.K., Wechsberg, W.M., Kline, T. L. & Ellerson, R. M. (2010). Health services utilization among South African women living with HIV and reporting sexual and substance-use risk behaviors. *AIDS Patient Care and STDs,* 24(4):257–64.

Marsh, J.C., Cao, D. & D'Aunno, T. (2004). Gender differences in the impact of comprehensive services in substance abuse treatment. *Journal of Substance Abuse Treatment,* 27(4):289–300.

Messina, N., Burdon, W. & Prendergast, M. (2006). Prison-based treatment for drug-dependent women offenders: treatment versus no treatment. *Journal of Psychoactive Drugs,* Suppl 3:333–43.

Morgan, M.Y. & Sherlock, S. (1977). Sex-related differences among 100 patients with alcoholic liver disease. *British Medical Journal*, 1(6066): 939–41.

Morojele, N.K., Flisher, A.J., Muller, M., Ziervogel, C.F., Reddy, P. & Lombard, C.J. (2002). Measurement of risk and protective factors for drug use and anti-social behavior among high school students in South Africa. *Journal of Drug Education*, 32(1):25–39.

Morojele, N.K., Kachieng'a, M.A., Mokoko, E., Nkoko, M.A., Parry, C.D., Nkowane, A.M., Moshia, K.M. & Saxena, S. (2006). Alcohol use and sexual behaviour among risky drinkers and bar and shebeen patrons in Gauteng province, South Africa. *Social Science & Medicine*, 62(1):217–27.

Myers, B. (2007). Access to substance abuse treatment for historically underserved communities in the Cape Town metropole. Technical report 2007.

Myers, B. & Fakier, N. (2007). Audit of substance abuse treatment facilities in KwaZulu-Natal and Gauteng. Technical report 2007.

Myers, B., Fakier, N. & Louw, J. (2009). Stigma, treatment beliefs, and substance abuse treatment use in historically disadvantaged communities. *African Journal of Psychiatry (Johannesburg)*, 12(3):218–22.

Niv, N. & Hser, Y.I. (2007). Women-only and mixed-gender drug abuse treatment programs: service needs, utilization and outcomes. *Drug and Alcohol Dependence*, 87(2–3):194–201.

Nixon, S.J., Tivis, R. & Parsons, O.A. (1995). Behavioral dysfunction and cognitive efficiency in male and female alcoholics. *Alcoholism: Clinical & Experimental Research,* 19(3):577–81.

Parry, C.D., Bhana, A., Myers, B., Plüddemann, A., Flisher, A.J., Peden, M.M. & Morojele, N.K. (2002). Alcohol use in South Africa: findings from the South African Community Epidemiology Network on Drug Use (SACENDU) project. *Journal of Studies on Alcohol*, 63(4):430–35.

Parry, C.D., Plüddemann, A., Steyn, K., Bradshaw, D., Norman, R. & Laubscher, R. (2005). Alcohol use in South Africa: findings from the first Demographic and Health Survey (1998). *Journal of Studies on Alcohol*, 66(1):91–97.

Plüddemann, A., Dada, S., Williams, Y., Bhana, A., Pereira, T., Carelsen, A., Gerber, W., Rosslee, C., Parry, C. & Fourie, D. (2009). Monitoring alcohol and drug abuse treatment admissions in South Africa. Feedback from the South African Community Epidemiology Network on Drug Use (SACENDU) project, Phase 25, July–December 2008. South African Medical Research Council.

Rawson, R.A., Gonzales, R., Pearce, V., Ang, A., Marinelli-Casey, P. & Brummer, J. (2008). Methamphetamine dependence and human immunodeficiency virus risk behavior. *Journal of Substance Abuse Treatment*, 35(3):279–84.

Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L. & Goodwin, F.K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) study. *Journal of the American Medical Association*, 264(19):2511–18.

Rehm, J. & Parry, C. (2009). Alcohol consumption and infectious diseases in South Africa. *Lancet*, 374(9707):2053.

Robinson, E.A., Brower, K.J. & Gomberg, E.S. (2001). Explaining unexpected gender differences in hostility among persons seeking treatment for substance use disorders. *Journal of Studies on Alcohol*, 62(5):667–74.

Sacks, J.Y., McKendrick, K. & Banks, S. (2008). The impact of early trauma and abuse on residential substance abuse treatment outcomes for women. *Journal of Substance Abuse Treatment*, 34(1):90–100.

Saunders, J.B., Davis, M. & Williams, R. (1981). Do women develop alcoholic liver disease more readily than men? *British Medical Journal (Clinical Research Edition),* 282(6270):1140–43.

Sawyer, K.M., Wechsberg, W.M. & Myers, B.J. (2006). Cultural similarities and differences between a sample of black/African and colored women in South Africa: convergence

of risk related to substance use, sexual behavior, and violence. *Women Health,* 43(2):73–92.

Schneider, M., Norman, R., Parry, C., Bradshaw, D. & Plüddemann, A. (2007). Estimating the burden of disease attributable to alcohol use in South Africa in 2000. *South African Medical Journal*, 97(8 Pt 2):664–72.

Schuckit, M.A., Daeppen, J.B., Tipp, J.E., Hesselbrock, M. & Bucholz, K.K. (1998). The clinical course of alcohol-related problems in alcohol dependent and nonalcohol dependent drinking women and men. *Journal of Studies on Alcohol*, 59(5):581–90.

Schuckit, M.A., Smith, T.L., Danko, G.P., Bucholz, K.K., Reich, T. & Bierut, L. (2001). Five-year clinical course associated with DSM-IV alcohol abuse or dependence in a large group of men and women. *American Journal of Psychiatry*, 158(7):1084–90

Simpson, M. & McNulty, J. (2008). Different needs: women's drug use and treatment in the UK. *International Journal of Drug Policy*, 19(2):169–75.

Somers, J.M., Goldner, E.M., Waraich, P. & Hsu, L. (2004). Prevalence studies of substance-related disorders: a systematic review of the literature. *Canadian Journal of Psychiatry*, 49(6):373–84.

Stewart, D., Gossop, M. & Trakada, K. (2007). Drug dependent parents: childcare responsibilities, involvement with treatment services, and treatment outcomes. *Addictive Behaviors*, 32(8):1657–68.

Stewart, S.H., Brown, C.G., Devoulyte, K., Theakston, J. & Larsen, S.E. (2006). Why do women with alcohol problems binge eat? Exploring connections between binge eating and heavy drinking in women receiving treatment for alcohol problems. *Journal of Health Psychology*, 11(3):409–25.

Strathdee, S.A. & Sherman, S.G. (2003). The role of sexual transmission of HIV infection among injection and non-injection drug users. *Journal of Urban Health*, 80(4 Suppl. 3): iii7–14.

Sun, W., Skara, S., Sun, P., Dent, C. W. & Sussman, S. (2006). Project Towards No Drug Abuse: long-term substance use outcomes evaluation. *Preventive Medicine*, 42(3):188–92.

Tucker, J.A., Vuchinich, R.E. & Rippens, P.D. (2004). A factor analytic study of influences on patterns of help-seeking among treated and untreated alcohol dependent persons. *Journal of Substance Abuse Treatment*, 26(3)237–42.

Uziel-Miller, N.D. & Lyons, J.S. (2000). Specialized substance abuse treatment for women and their children: an analysis of program design. *Journal of Substance Abuse Treatment*, 19(4):355–67.

Wechsberg, W.M., Luseno, W.K. & Lam, W.K. (2005). Violence against substance-abusing South African sex workers: intersection with culture and HIV risk. *AIDS Care*, 17(Suppl. 1): S55–S64.

Wechsberg, W.M., Luseno, W.K., Lam, W.K., Parry, C.D. & Morojele, N.K. (2006). Substance use, sexual risk, and violence: HIV prevention intervention with sex workers in Pretoria. *AIDS and Behavior,* 10(2):131–37.

Wechsberg, W.M., Luseno, W., Riehman, K., Karg, R., Browne, F. & Parry, C. (2008). Substance use and sexual risk within the context of gender inequality in South Africa. *Substance Use & Misuse*, 43(8-9):1186–201.

Wechsberg, W.M., Wu, L.T., Zule, W.A., Parry, C.D., Browne, F.A., Luseno, W.K., Kline, T. & Gentry, A. (2009). Substance abuse, treatment needs and access among female sex workers and non-sex workers in Pretoria, South Africa. *Substance Abuse Treatment, Prevention, and Policy*, 4:11.

Wenzel S.L., Audrey Burnam, M., Koegel, P., Morton, S.C., Miu, A., Jinnett, K.J., Greer Sullivan, J. (2001). Access to inpatient or residential substance abuse treatment among homeless adults with alcohol or other drug use disorders. *Medical Care*, 39(11):1158–69.

World Health Organization (WHO). (2009). Copenhagen: WHO Regional Office for Europe.

Wilsnack, S.C., Klassen, A.D. & Wilsnack, R.W. (1984). Drinking and reproductive dysfunction among women in a 1981 national survey. *Alcoholism: Clinical & Experimental Research*, 8(5):451–58.

Zumoff, B. (1997). Alcohol, estrogens, and breast cancer. *The Journal of Clinical Endocrinology & Metabolism*, 82(7):2378.

Neuroscience and Psychiatry

5 Addiction as virtual seeking: evolutionary insights into addiction

David Kibel and Dan J. Stein

Introduction

The vast majority of current medical and psychiatric research focuses on 'proximal' mechanisms – the underlying psychobiological mechanisms, including psychological and neurobiological processes, that contribute to the onset or maintenance of disorders. However, there is growing interest in both medicine and psychiatry in the relevant 'distal' mechanisms – the evolutionary mechanisms that play a role in these conditions. *Why We Get Sick: The New Science of Evolutionary Medicine* (1994) by R.M. Nesse and G.C. Williams played a seminal role in this field, and has been followed by a number of textbooks which present a wealth of new theoretical and empirical knowledge.

An evolutionary approach may also be useful in understanding substance use disorders. Once again, Nesse played a key role in encouraging this view, publishing a seminal paper on the topic with Berridge, an article which argued that drugs that induce positive emotions act on ancient brain mechanisms that control emotion and behaviour, and give a false signal of a fitness benefit (Nesse & Berridge, 1997). However, a range of other authors have also contributed to this area and consolidated an evolutionary approach to substance use disorders (Pomerleau, 1997; Gerard & Higley, 2002). In this chapter, we briefly discuss relevant literature in this area, and make the claim that addiction can be understand as 'virtual seeking behaviour'.

The term 'virtual' emphasises the idea that addictive substances act on the brain's reward system (including both its 'liking' and its 'wanting' components), but that these do not in fact involve real-life rewards. The term 'seeking' derives from Panksepp's work (1998), where it refers to a key mammalian motivation system (not dissimilar in conceptualisation from the 'wanting' component of the reward system) which enables animals to find fitness opportunities and solutions to recurring survival challenges in the real world (although the argument here does not require a complete acceptance of the details of this work).

The conjunction of the two terms 'virtual' and 'seeking' emphasises both the strength of the mechanisms involved in substance use disorders (with substances co-opting evolutionary ancient and key mechanisms of survival) and their ultimate futility (given that the subjectively experienced rewards are delinked from those derived from living in the world; they are narrow and transient, and in effect evade adaptive real-life solutions). This kind of disjuncture between narrow subjective experience and broader lived reality, reminds the authors of Magritte's painting, *The Human Condition*, of looking through a window onto a represented depiction of life, rather than participating in it.

Conservation of key systems, including the motivation system

Mammalian central motivational or brain reward systems help regulate bodily homeostatis, and appear to be divided into distinct appetitive ('wanting' or seeking) and consummatory ('liking') components. The 'wanting' component refers to behavioural pursuit of a goal, and involves the mesolimbic dopaminergic system. The 'liking' component refers to the hedonic pleasure of receiving a reward, and is mediated by forebrain opioid systems. Thus, the search for the desired goal is terminated by a consummatory phase, followed by a quiescent period until the cycle begins again. It is possible that a separate system evolved for 'wanting' so that various 'likes' (eg, for food, sex) could be carefully evaluated.

Given the key role the reward system plays in animals, it is not surprising that it is highly conserved. Certainly, the mammalian reward system has a similar neuroanatomy, with similar neurochemical underpinnings, across a range of species. Studies of the nucleus accumbens and the dopamine system in rodents and non-human primates are therefore able to shed considerable light on how particular neuronal circuits and their component neurotransmitters modulate incentive motivation in humans. The use of dopamine by reward systems is particularly ancient; dopamine mediates feeding even in invertebrates. Mu-opioid receptor-like DNA sequences have been found in most vertebrate brains.

Substances of abuse act selectively on these evolutionarily conserved brain substrates. This is evidenced by the remarkable fact that other mammals quickly exhibit compulsive self-administration of precisely the same drugs as are seen in human substance use disorders. Nesse and Berridge have argued that when the 'wanting' and 'liking' systems are exposed to substances, the 'wanting' system motivates persistent pursuit, despite the lack of pleasure, accounting for a core paradox in addiction. Although there are undoubtedly particularly 'human' aspects of the phenomenology and psychobiology of substance use disorders, we can learn a great deal about ourselves, and our propensity to abuse substances, by close examination of animal models of addiction.

Evolutionary theory and explanations of disease

By elaborating distal, evolutionary mechanisms, evolutionary theory provides a useful approach to understanding disease, one which complements our growing understanding of the biochemical and physiological mechanisms that underpin illnesses. An important principle to note is that although the body is exquisitely designed, it is far from perfect. For example, the evolution of human bipedal locomotion provides humans with many advantages, including the ability to run further than other mammals over long distances (Bramble & Lieberman, 2004). On the other hand, our vertebrae are particularly prone to a whole range of medical disorders, including prolapse.

One concept often used in evolutionary medicine is that of 'mismatch'. Our bodies are optimised to function in the 'environment of evolutionary adaptedness'. However, modern life brings with it an entirely different context, and this mismatch may result in a range of problems. Thus, for example, our bodies have evolved to have a preference for sweet and salty foods, an adaptive choice in environments where food resources are constrained. In the modern environment, where refined foods are cheaply available, an epidemic of obesity

has occurred. Similarly, our brains are not adapted to cope with addictive substances, which 'hijack' incentive motivational systems.

Psychoactive drugs work either by giving a false signal of impending fitness benefits (opportunities) or by blocking fitness loss (blocking defences, eg, pain and anxiety) (Nesse & Berridge, 1997). Substances of abuse, for example, act on the SEEKING system, so that the organism anticipates reward, and attempts to ingest more of the substance. Substance ingestion may lead to transient hedonic pleasure, but in fact such behaviour is maladaptive, insofar as the real demands of the environment cannot be addressed. Increasing public awareness of the nature of substance use as 'virtual seeking' may be a key step in preventive efforts, and a model such as this one may also serve as a useful explanatory model at the time of initiating treatment.

Another evolutionary model has emphasised the adaptive value of certain traits often seen in substance users. In resource-scarce environments, a 'live-fast-die-young' strategy may be particularly adaptive for individuals who have little emotional or material support. Gerard and Higley (2002) have drawn parallels between this phenotype and Cloninger Type 2 alcoholics (who display early onset, antisocial behaviour, impaired social function, high novelty and low harm-avoidance), and emphasise the role of the serotonin system in both impulsive-aggression and alcoholism. Other work has emphasised additional systems. For example, the dopamine system is key in the trait of novelty-seeking (Wang et al, 2004).

The SEEKING system: understanding its role in addiction

Panksepp (1998) describes the SEEKING system as a distinct general-purpose system for all appetitive searches. The system is mediated by neurons that project from the ventral tegmental area (VTA) to the lateral hypothalamic and then to the mesolimbic-mesocortical tract (see Figure 2 in the Introduction). The SEEKING system is accessed by all homeostatic needs but is *to some extent independent of normal homeostatic imbalances* (authors' emphasis). Indeed, some needs are so crucial, and the resource so readily available (for example, oxygen), that evolution has automated the process of breathing and eliminated choice. Most other needs require an active exploratory search and prioritising of choice.

However, the SEEKING system is responsive in the anticipatory phase of reward, more than the reward itself, and is most activated under conditions of uncertainty (Fiorillo et al, 2003). This accounts for why unpredictable intermittent reinforcements (and punishments) become profoundly reinforcing (or stressful). Indeed, the special characteristics of the SEEKING system, and the neuronal sensitisation that occurs in dopaminergic projections after exposure to substances, help explain a number of key features of substance use disorders, including rapid acquisition, the increased intensity needed to achieve the desired effect, and the worsening of substance use disorders under conditions of stress.

Dopamine stimulants such as cocaine act – at supraphysiological levels – directly on the SEEKING system, providing a window into the subjective feelings evoked within the system, feelings of excitement and anticipation related to reward anticipation. This is in contrast to the subjective experience of opiates such as heroin, which induce a feeling of satisfaction or consummatory pleasure. Chronic over-stimulation of the SEEKING system by substances overrides consummatory feedback loops, leading to a state of chronic wanting (a 'thirst

that can never be quenched'). This leads to disorganisation or decoupling of appetitive/consumptive phases of reward systems. Pharmacological modulation of these systems may therefore be an important treatment consideration.

Substance use and allostatic overload: a vicious cycle

Allostasis can be defined as the ability to adapt to changing levels of stress or threat, and can be conceptualised as deriving from an evolutionarily older homeostatic ability to maintain bodily systems intact in response to a varying environment. Homeostatic systems (eg, those modulating pH, temperature) are characterised by regulation of a specific set point. Allostatic systems (eg, stress response systems, pain systems), on the other hand, have an adaptive range rather than a particular set point, are vulnerable to overload, and reflect an exquisite link to our social milieu (eg, success, failure) allowing us to adapt to a constantly changing world.

Substance use disorders reflect a state of allostatic overload (in common with major depression), with consequent damaging metabolic effects on the body, and in particular the brain. This arises in part because those suffering from these conditions are caught in a web of salient cues, constant drug-seeking (craving) and withdrawal, resulting in a vicious cycle of ever-increasing impairment. Stressors may lead to an increase in substance abuse, and impairment caused by such abuse may lead to an increase in stressors.

Evolutionary theory predicts that certain events are particularly stressful: social isolation or loss of attachment, unaccepted loss of rank or support, and uncertainty and unpredictability. In response to such stressors, it may be adaptive to alter one's physiological response to the environment, to ensure increased salience to environmental threat. On the other hand, individuals may be vulnerable to allostatic overload by virtue of genetic factors and a range of stressors, including early life experiences. Part of the treatment of substance use disorders involves psychotherapy, with identification of stressors that trigger relapse, and learning more adaptive responses to stressors.

Encephalisation, neuroplasticity and human choice

Although evolutionary theory emphasises the conservation of important homeostatic and allostatic systems across species, it also provides key insights into cross-species differences. A particularly important difference between rodents, non-human primates and humans is the degree of encephalisation. In primates, increasingly sophisticated cognitive-affective systems are available for responding to the environment. These allow the organism to develop a broad range of adaptive responses to challenges. The evolution of the prefrontal cortex in humans appears to have given a huge advantage via an ability to capture and retain information over longer and longer periods of time, allowing the development of hindsight, foresight and memory.

An important theme in addiction is an inability to learn from past experience (ie, extract the main theme, repeating the same damaging behaviours). The disinhibiting effects of alcohol quickly corrode any carefully reasoned rationale and intention to keep clean, opening the doors to other addictions (alcohol and cocaine, alcohol and sex/love addiction).

Similarly, individuals with frontal lobe injury are vulnerable to substance use disorders. Furthermore, during the process of addiction, there is often self-deception. At the same time, our prefrontal capacity for weighing up different options may be central in allowing treatments that focus on understanding factors which promote substance use, and on developing more flexible responses.

A number of treatment approaches to substance use disorders place significant emphasis on choice. There is also a growing understanding of neuroplasticity, and possibilities for learning new choices. There is constant learning and unlearning taking place in the brain to allow new skills, new identities, new attachments. In recovery from addiction, a process of relearning takes place. The brain changes necessary to accommodate the drug itself, drug-associated behavioural patterns and psycho-social consequences of using take time to repair and unlearn. This can be a relatively long process as old skills are revived, neglected relationships resurrected, new coping skills learned, new attachments formed and identities established. The AA adage, 'one day at a time', appears apposite.

Conclusion

In conclusion, evolutionary principles may be useful in conceptualising substance use disorders. We have emphasised their relevance to clinical treatment of substance use disorders. Evolutionary medicine has received significant criticism on the grounds that it tells 'just so' stories (Wright, 1995) which cannot be proven or disproven. Nevertheless, we hope that by grounding our argument within contemporary evolutionary theory and empirical neuroscience, and by spelling out some of the practical implications of an evolutionary psychiatry approach to substance use disorders, we have provided a useful perspective.

References

Bramble, D.M. & Lieberman, D.E. (2004). Endurance running and the evolution of Homo. *Nature*, 432(7015):345–52.

Fiorillo, C.D., Tobler, P.N. & Schultz, W. (2003). Discrete coding of reward probability and uncertainty by dopamine neurons. *Science*, 299(5614):1898–902.

Gerard, M.S. & Higley, J.D. (2002). Evolutionary underpinnings of excessive alcohol consumption. *Addiction*, 97(4):415–25.

Nesse, R.M. & Berridge, K.C. (1997). Psychoactive drug use in evolutionary perspective. *Science*, 278(5335):63–66.

Nesse, R.M. & Williams, G.C. (1994). *Why We Get Sick: The New Science of Darwinian Medicine*. New York: Vintage Books.

Panksepp, J. (1998). *Affective Neuroscience: The Foundations of Human and Animal Emotions*. Oxford: Oxford University Press.

Pomerleau, C.S. 1997. Co-factors for smoking and evolutionary psychobiology. *Addiction*, 92(4):397–408.

Wang, E., Ding, Y.C., Flodman, P., Kidd, J.R., Kidd, K.K., Grady, D.L., Ryder, O.A., Spence, A.A., Swanson, J.M. & Moyzis, R.K. (2004). The genetic architecture of selection at

the human dopamine receptor D4 (DRD4) gene locus. *The American Journal of Human Genetics*, 74(5):931–44.

Wright, R. (1995). *The Moral Animal: Why We are the Way We Are. The New Science of Evolutionary Psychology*. New York: Vintage Books.

6 Genetics and molecular biology

Shareefa Dalvie and Fleur Howells

Introduction

Family, adoption and twin studies strongly suggest that addiction has high heritability (between 30 and 60%) (Kreek et al, 2005). Heritability is a measurement of the proportion of the disease phenotype, which is a consequence of the genetic composition (Lewis, 2001). Different heritability values are observed for addiction to different classes of substances. For example, addiction to cocaine and other opiates has a higher heritability compared to hallucinogens. The absence of a clear Mendelian pattern of inheritance in families suggests that this type of complex disorder is as a result of inheritance of numerous genetic variations (Goldman et al, 2006). Linkage and association studies have identified susceptibility regions and genes for alcohol and nicotine dependence. However, these results have proven difficult to replicate in independent samples (Li et al, 2009). More recently, genome-wide linkage and association studies have identified regions in the genome which may impart small effects to phenotype vulnerability. Most genes implicated in substance abuse or addiction function in the dopaminergic system, thus reinforcing the importance of this system in the development of substance abuse/addiction.

Dopamine

The major neurotransmitter system implicated in drug use and abuse is the dopaminergic system, as the activation of this system is related to mechanisms of reward, motivation and reward-seeking behaviours (Wise, 2005).

The nuclei bodies of the dopaminergic system are located in the brainstem, comprising the ventral tegmentum and the substantia nigra (see Figure 6.1). The main subcortical structure known to play a key role in processes related to drug addiction, including both molecular sensitisation (Kalivas et al, 1991; Robinson et al, 1986) and synaptic modification, is the nucleus accumbens (Hyman, 2005; Tully et al, 2003; Ungless et al, 2001; Wise, 2004). The nucleus accumbens receives dopaminergic input from both the VTA and, to a lesser degree, the substantia nigra (Wise, 2009). There are two functional sections within the nucleus accumbens: the core and the shell (see Figure 6.2). The core shows greater release of dopamine, in response to acute administration of cocaine, amphetamine or morphine, than the shell. Cannabis and nicotine have been shown to increase the release of dopamine within the nucleus accumbens through indirect pathways.

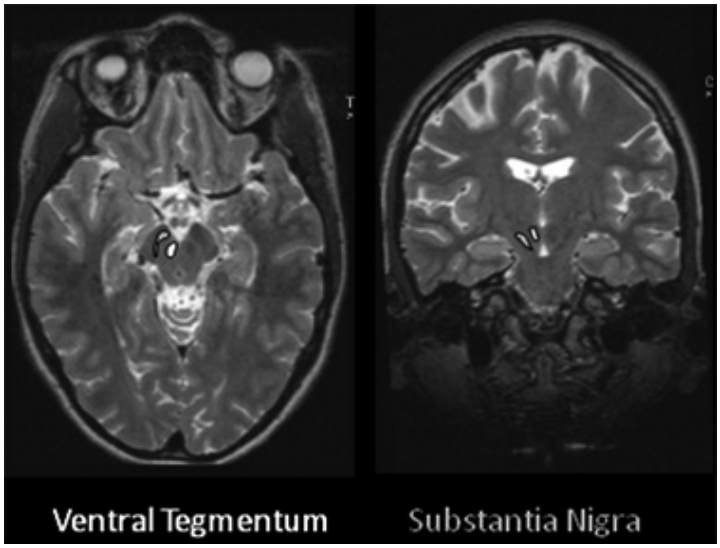

Figure 6.1: Axial and coronal view of the ventral tegmentum and substantia nigra from a T2-weighted MRI scan

Source: Figure created by Howells

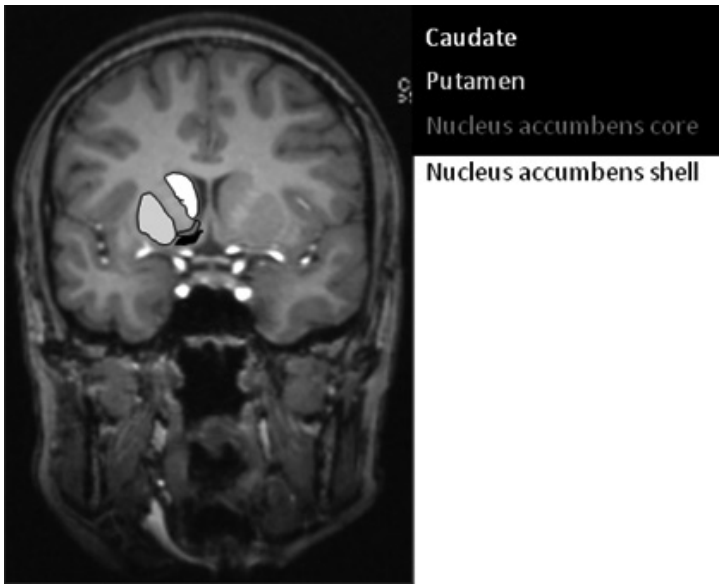

Figure 6.2: Coronal view of the striatum (caudate and putamen) and the nucleus accumbens (core and shell) from a T2-weighted MRI scan

Source: Figure created by Howells

Dopamine is synthesised in the presynaptic terminal of the presynaptic neuron through a cascade of enzymatic reactions. Phenylalanine is hydroxylated to form tyrosine (tyrosine hydroxylase, the rate-limiting enzyme), which is subsequently hydroxylated to L-dopa. L-dopa is then decarboxylated to form dopamine (Ganong, 2001; Kandel et al, 2000) (see Figure 6.3). Dopamine is classed as a catecholamine due to it having a catechol nucleus and a 3.4-dihydroxylated benzene ring. Norepinephrine and epinephrine are also catecholamines, and dopamine is required for their synthesis (Kandel et al, 2000). Dopamine, once synthesised, is packaged into dopamine-specific vesicles (VMAT) (Fon et al, 1997; Takahashi et al, 1997; Wang et al, 1997). Upon depolarisation of the dopaminergic presynaptic terminal, the dopamine-containing vesicle docks onto the presynaptic membrane and is subsequently released into the synaptic cleft through a process of exocytosis. Decreased expression of VMAT2 has been related to chronic use of methamphetamine and rapid sensitisation to psychostimulants (Johanson et al, 2006; Wang et al, 1997).

Binding of dopamine to either D1 or D5 receptors leads to activation of a G protein (Gs), which is responsible for activating the enzyme adenylyl cyclase (see Figure 6.3). This enzyme converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Furthermore, cAMP activates protein kinase A (PKA) by attachment to the inhibitory regulatory subunit, thus releasing the active catalytic subunit. This catalytic subunit of PKA acts along three pathways: (1) phosphorylation of K^+ channels, leading to prolonged depolarisation due to continued activity of Ca^{+2} channels; (2) enhancement of vesicle docking and neurotransmitter release; (3) opening of L-type Ca^{+2} channels, further prolonging the depolarisation of the terminal (Kandel et al, 2000).

D1 receptor knockout mice show decreased psychostimulant responsiveness (Xu et al, 1994) and cocaine sensitisation (Xu et al, 2000). In these mice, after the initial sensitisation of the terminal, early immediate genes are activated through phosphorylation of the transcription factor, cAMP response element binding protein (CREB). This leads to increased expression of Fos, Jun, and ΔFosB (Nestler, 2002; Walters et al, 2003). The induction of these genes is rapid and mostly transient. Increased ΔFosB expression has been strongly related to increased behavioural response, duration and intensity of sensitisation to cocaine and amphetamine (McClung et al, 2004) and decreased sensitivity of the nucleus accumbens neurons to glutamate (Peakman et al, 2003). To date, D5 receptor knockouts have failed to show similar effects in sensitisation to drugs of abuse (Elliot et al, 2003).

Binding of dopamine to D2, D3 or D4 receptors leads to activation of a G protein (Gi) which inhibits adenylyl cyclase. D2 receptors, found primarily on presynaptic terminals, are autoreceptors (see Figure 6.3). Activation of the D2 receptors leads to shortened periods of depolarisation and decreased release of neurotransmitter (Kandel et al, 2000). Mechanisms following the activation of D2 receptors therefore compete with the activities of D1 receptors, presynaptically, thus reducing the sensitisation (Beaulieu et al, 2007). PET, SPECT and histochemical human studies have clearly demonstrated reduced D2 receptor density in the striatum of addicts of cocaine, methamphetamine and alcohol, even after detoxification (Guardia et al, 2000; Matsumoto et al, 2001; Volkow et al, 2001, 2004a, 2004b).

It is suggested that reduced D2 receptor density relates to a low dopamine tone, and individuals with decreased density of D2 receptors may self-medicate with drugs of abuse to increase the activity of their lethargic dopamine systems (Comings et al, 1994,

2000). The D2 receptor gene (*DRD2*) is located on chromosome 11, at q22–q23, and is comprised of two alleles: A1 and A2 (Grandy et al, 1989), distinguished by the Taq1A, a non-functional restriction fragment length polymorphism (RFLP) located downstream of the *DRD2* gene. This polymorphism has been associated with polysubstance abuse (O'Hara et al, 1993) and age of onset of substance abuse (Comings et al, 1994). In addition, the *DRD2* Taq1A polymorphism has been related to cocaine, methamphetamine, alcohol and nicotine addiction (Connor et al, 2002; Huang et al, 2007; Konishi et al, 2004; Lerman et al, 1999; Limosin et al, 2002; Noble et al, 1993; Persico et al, 1996; Sabol et al, 1999; Willis-Owen et al, 2005). Individuals who have the A1 allele of the *DRD2* Taq1A polymorphism have reduced D2 receptor density (Jonsson et al, 1999; Noble et al, 1991; Noble et al, 1997; Noble, 2003; Pohjalainen et al, 1998). In 2008, a meta-analysis study, found that the A1 allele of the *DRD2* Taq1A polymorphism has a small, but significant, association with alcohol dependence, and that many previously conflicting results were due to small sample sizes and different sample selection criteria. The authors suggested that it is highly likely that complex disorders such as alcohol dependence are as a result of a multi-gene effect (Smith et al, 2008). In a family study, Hill et al (2008) identified an association between a polymorphism (C957T), located in the coding region of the *DRD2* gene, and alcohol dependence (Hill et al, 2008). It was also demonstrated that this single nucleotide polymorphism (SNP) and the Taq1A polymorphism may have an effect on the development of dissociative personality disorders and psycho-social behaviours in alcohol-dependent individuals (Ponce et al, 2008). In addition, variants within *DRD2* have also been implicated as risk factors for a more severe prognosis for methamphetamine abuse. The –141C insertion/deletion polymorphism within this gene has been associated with a more rapid onset of psychosis within three years following methamphetamine abuse (Ujike et al, 2009) as well as alcoholism (Konishi et al, 2004).

D3 and D4 receptors have been implicated in vulnerability to substance abuse. Not all studies, however, support this association (Goodman, 2008; Vandenbergh et al, 2000). Disruption of these receptors results in enhanced acute response to cocaine (Carta et al, 2000; Katz et al, 2003; Rubinstein et al, 1997; Xu et al, 1997). Haplotype analysis has revealed an association between a 120bp variable number tandem repeat (VNTR) in the promoter region, and a 48bp VNTR in exon 3, of the D4 receptor gene (*DRD4*), and methamphetamine abuse (Li et al, 2004). Also, adolescents with the 7-repeat allele of the 48bp VNTR have an increased risk of drinking greater volumes of alcohol, and have a higher lifetime risk of alcohol abuse, compared to adolescents with a different number of alleles (Laucht et al, 2007).

Dopamine is packaged into dopamine specific vesicles (VMAT). When the presynaptic nerve terminal is excited (depolarisation), dopamine is released through docking of dopamine vesicles to the presynaptic membrane, and dopamine is released into the synaptic cleft through exocytosis. The dopamine released into the synaptic cleft then diffuses. The receptors on the postsynaptic membrane are either excitatory (D1/D5) or inhibitory (D3/D4) and activate G proteins that are coupled to the receptors inside the postsynaptic membrane. The presynaptic membrane is able to regulate the release of dopamine through activation of D2 receptors that are inhibitory and decrease the excitability of the presynaptic membrane. In addition, the concentration of dopamine in the synaptic cleft is cleared through the reuptake of dopamine through dopamine transporters (DAT).

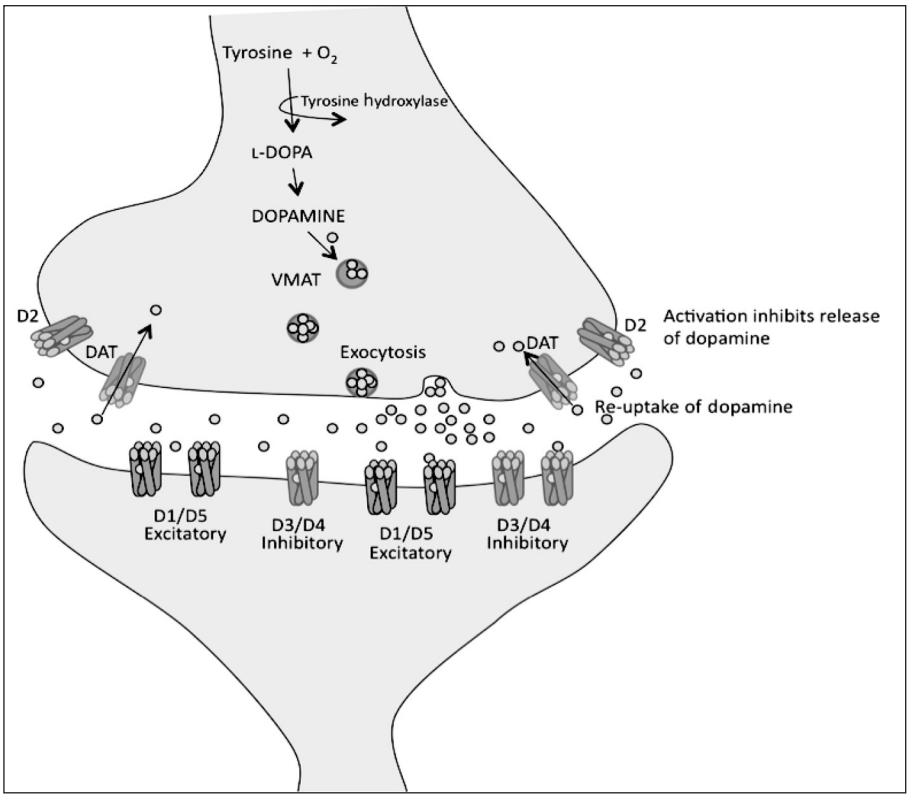

Figure 6.3: Synthesis of dopamine in the presynaptic neuron, regulated by the rate-limiting enzyme tyrosine hydroxylase

Source: Figure created by Howells

Reuptake of dopamine that has not bound to a receptor, ie, the residual transmitter, is taken up by dopamine transporter (DAT) on the presynaptic terminal (see Figure 6.3). This sequestering of dopamine reduces, or shortens, the duration of dopamine activity in the synapse. In addition, the reuptake of dopamine allows repackaging of the dopamine into vesicles that are close to the presynaptic membrane, where they are then ready for the next depolarisation (Glowinski et al, 1966; Snyder et al, 1969). Cocaine, methamphetamine and amphetamine both increase the synaptic concentration of dopamine within the nucleus accumbens by directly blocking DAT (Kandel et al, 2000; Ritz et al, 1987). Methamphetamine, in addition, has been suggested to reverse dopamine transport through DAT (Goodwin et al, 2009). Alcoholics show decreased DAT availability (Heinz et al, 2001). Reduced expression of DAT has been shown to increase the tone of dopamine within the synaptic cleft (Giros et al, 1996; Jones et al, 1998). Reduced expression of DAT increases cocaine- and amphetamine-conditioned place preference with treatment and after treatment (over 55 days) with amphetamine (Budygin et al, 2004; Rocha et al, 1998; Sora et al, 1998). Of interest, DAT knockout mice, and DAT-blocked wild-type mice, show adaptive changes

in their serotonergic systems within the VTA. Increased serotonin in the VTA increases the firing rate of the VTA through activation of serotonin 2 receptors (Pessia et al, 1994), leading to indirect release of dopamine in the nucleus accumbens (Mateo et al, 2004). Serotonin has been effective in cocaine and amphetamine reward processes (Budygin et al, 2004; Rocha et al, 1998; Sora et al, 1998). Genetic associations between the gene that encodes DAT, *SLC6A3*, and cocaine addiction have been suggested (Gelernter et al, 1994).

Dopamine may be catabolised (broken down) by mitrochrondrial flavoenzyme monoamine oxidase (MAO). MAO activity is decreased in alcoholics (Gottfries et al, 1975; Major et al, 1978; Major et al, 1981; Oreland et al, 1983). After initial withdrawal from alcohol, alcoholics have an immediate increase in MAO, which returns to decreased levels by the third week of abstinence (Major et al, 1981; Wiberg, 1979).

Norepinephrine

An important neurotransmitter system that regulates the activity of the ascending dopaminergic neurons is the locus coeruleus norepinephrine system. This has been shown to enhance dopaminergic system activity during the reward processes of psychostimulant abuse (Yamamoto et al, 1998). In addition, it has been suggested that with psychostimulant abuse, the release of norepinephrine is greater than that of dopamine (Rothman et al, 2001).

The locus coeruleus, which is composed of noradrenergic neurons, projects to the VTA (Grenhoff et al, 1993) and the nucleus accumbens, as well as to the prefrontal cortex, where it modulates dopaminergic projection activity (Gresch et al, 1995). Electrical stimulation of the locus coeruleus increases cortical norepinephrine and dopamine levels (Devoto et al, 2005). Norepinephrine is synthesised from dopamine, and is also classed as a catecholamine. Dopamine is hydroxylated by the enzyme dopamine-β-hydroxylase (DβH) to form norepinephrine. This conversion takes place in noradrenergic transmitter vesicles (Ganong, 2001; Kandel et al, 2000). DβH is stable in plasma, and plasma levels of this enzyme are related to spinal fluid concentrations. DβH inhibitors reduced the production of norepinephrine and decreased reinforcement of amphetaminine self-administration in rats (Davis et al, 1975).

Cortical activation of α_1-adrenoceptors (norepinephrine alpha receptors) increases dopamine release in the NAc, and increases the behavioural locomotor effect of amphetamine (Darracq et al, 1998). Injection of an α_1-adrenoceptor antagonist (prazosin) into the cortex, or systemically, reduces the release of dopamine in the NAc, and reduces the behavioural locomotor effect of cocaine and amphetamine (Blanc et al, 1994; Darracq et al, 1998; Drouin et al, 2002; Zhang et al, 2005). α_{1B}-adrenoceptor knockout mice show decreased drug-induced locomotor activity (Drouin et al, 2002). It has been suggested that norepinephrine modulates these changes through a cortical to nucleus accumbens glutamatergic pathway, and that this pathway is related to the reinstatement of drug-seeking behaviour (Kalivas et al, 2003). The α_2-adrenoceptors are primarily autoreceptors located on presynaptic varicosities of the noradrenergic neurons. Decreasing norepinephrine concentrations by supplying an agonist to the α_{2A}-adrenoceptor (lofexidine) was shown to reduce ethanol self-administration in rats (Le et al, 2005). Furthermore, increasing norepinephrine concentrations by supplying an

antagonist to the α_{2A}-adrenoceptor (yohimbine or RS-79948) reinstated cocaine-seeking in rats (Lee et al, 2004). Norepinephrine that is not bound to adrenoreceptors is sequestered by norepinephrine transporters (NET). NETs are also capable of reuptake of dopamine (Devoto et al, 2001). NET knockout mice lack the ability to reuptake norepinephrine and thus have elevated levels of norepinephrine. These mice self-administer cocaine four-fold the amount of wild-type mice (Rocha, 2003). A study conducted on a Han Chinese population found that the G1278A in exon 9 and the 5' promoter T-128C polymorphisms within the *NET* gene do not have an association with alcohol dependence. However, this does not preclude the *NET* gene from being involved in alcohol dependence, as other polymorphisms within this gene still need to be explored (Huang et al, 2008).

Serotonin

In general, serotonin is seen as a major player in behavioural inhibition (Goodman, 2008). Low levels of serotonin have been associated with increased impulsivity, which is suggested to underlie aspects of substance abuse and childhood alcoholism (Linnoila et al, 1983), while increased levels of serotonin have been shown to attenuate the effects of psychostimulants on the dopaminergic system (Rothman et al, 2006). In hand with these findings, it has been suggested that serotonin may serve as part of an agonist therapy to reduce addictive behaviours (Rothman et al, 2008). Serotonin is a monoamine neurotransmitter, as it contains one amino group connected to an aromatic ring by a two-carbon chain ($-CH_2-CH_2-$). Serotonin is synthesised from an essential amino acid, tryptophan. There are several brain nuclei that synthesise serotonin (5-HT), the major nuclei being the raphe nuclei of the brain stem (Kandel et al, 2000).

There are at least 14 subtypes of serotonin receptors: 5-HT_1 class is inhibitory, while 5-HT_4, 5-HT_5 and 5-HT_6 classes are excitatory, which are G-protein. Both these types are G-protein coupled. The 5-HT_3 class, when activated, acts as an excitatory ion channel (Goodman, 2008). The classes are divided by type $_{A\text{-}C}$. 5-HT_{1B} receptors are found on axon terminals of GABAergic interneurons that project from the nucleus accumbens to the VTA (David et al, 2004; Guan et al, 1989; Yan et al, 2004). With release of serotonin, the 5-HT_{1B} receptors inhibit the GABAergic terminal, disinhibiting the VTA. This inhibition of GABAergic neurons has been shown to increase levels of dopamine in response to cocaine and other rewarding or salient substances (David et al, 2004; Guan et al, 1989; Yan et al, 2004). This suggests that down-regulation of 5-HT_{1B} receptors on GABAergic axon terminals may reduce the development of addiction. Application of serotonin into the VTA increases the firing rate of the VTA, possibly through activation of 5-HT_2 receptors on the VTA dopaminergic neurons (Pessia et al, 1994). Serotonin is sequestered into the presynaptic neuron through the serotonin reuptake transporter (SERT). Reduced density of SERT was found in methamphetamine addicts, and was positively related to the duration of abuse (Sekine et al, 2006). The serotonin transporter-linked (*5-HTT*) polymorphic region (*5-HTTLPR*), located on chromosome 17 has been thoroughly investigated for association with drug and alcohol addiction. This region contains a 44bp insertion/deletion polymorphism, which results in a short (*S*) allele or long (*L*) allele. The *S* allele is thought to decrease the activity of the 5-HTT promoter, resulting in lower levels of *5-HTT* mRNA and decreased 5-HT uptake.

The *L* allele has the opposite effect on *5-HTT* expression (Lesch et al, 1996). The *S* allele has been shown to be significantly more prevalent in alcoholics and drug addicts as compared to controls (Gerra et al, 2004; Konishi et al, 2004; Lichtermann et al, 2000; Munafo et al, 2005; Sander et al, 1997). Meta-analyses of this polymorphism demonstrated that the *S*-allele is significantly associated with alcohol dependence (McHugh et al, 2010), and this association was significantly more profound in individuals with comorbid psychiatric diagnosis or a more severe phenotype (Feinn et al, 2005). However, definitive conclusions pertaining to the *5-HTTLPR* polymorphism cannot be drawn, as these findings could not be replicated (Dick et al, 2007; Edenberg et al, 1998; Kohnke et al, 2006; Rasmussen et al, 2008).

Glutamate

Glutamate is the central nervous system's major excitatory neurotransmitter. Glutamate is a non-essential amino acid. As a neurotransmitter it is released from neurons and supporting cells called glia. Glutamatergic neurons, from the prefrontal cortex and other limbic regions, innervate both the VTA and the nucleus accumbens. In these areas, glutamate either drives dopamine activity or modulates the neuronal activity of neurons with dopamine receptors (Carr et al, 2000). Its receptors are broadly defined as non-NMDA, NMDA and metabotropic glutamate receptors. Non-NMDA receptors include AMPA and kainate receptors. When these receptors are activated, they elicit fast excitatory postsynaptic potentials (EPSPs) through rapid influx of Na^+ ions (Kandel et al, 2000; Takahashi, 2005). AMPA receptors are fast-adapting in the sense that they are capable of rapid desensitisation or internalisation (Attwell et al, 2005; Rusakov et al, 1998), and are able to translocate to the surface of the postsynaptic terminals (Ashworth-Preece et al, 1999). Desensitisation and internalisation of AMPA receptors reduces the excitability of the postsynaptic terminal, while translocation of AMPA receptors to the membrane surface permits reinforcement of pathway(s) in which they are involved (Attwell et al, 2005; Derkach et al, 2007). Activation of D1 receptors has been shown to increase externalisation and increase activity of AMPA receptors (Wolf et al, 2004). Increased AMPA receptor number is seen in the initiation of long-term potentiation. This has been shown in the VTA and nucleus accumbens (Sutton et al, 2003). AMPA receptors are heteromers of glutamate receptor subunits GlurR1 through 4. The GluR1 subunit has been shown to increase during behavioural sensitisation with cocaine and ethanol (Churchill et al, 1999; Ortiz et al, 1995; Vekovischeva et al, 2001). However, long-term potentiation requires a second glutamatergic signal, which is afforded by the NMDA receptors.

The NMDA receptors require coincidence for their activation. Depolarisation of the nerve terminal on which they are found is needed prior to the opening of their ion channels. This is made possible by activation of AMPA receptors (Paoletti et al, 2007). When activated, NMDA receptors allow large influxes of Ca^{+2} and Na^+ into the synaptic terminal. The terminal activities of NMDA receptors are temporally longer than those of non-NMDA receptors (Derkach et al, 2007; Paoletti et al, 2007). Calcium entry leads to a cascade of events, including internalisation and translocation of non-NMDA receptors in the depolarised terminal membrane (Lee et al, 2003). Preventing the activity of NMDA receptors with NMDA

antagonists has been shown to prevent drug-induced long-term potentiation, which suggests that the development of drug addiction is dependent on neuronal plasticity (Chen et al, 2008). This goes in hand with down-regulation (decreased number) of NMDA receptors that occurs with age, and decreased synaptic plasticity, which includes long-term potentiation (Takahashi, 2005). NMDA receptor antagonists have been proposed as a potential therapy in relapse and withdrawal prevention (Bisaga et al, 2000). Functional NMDA receptors are composed of heteromers of the requisite NR1 subunit, which is expressed through the CNS, NR2 subunits A-D, which have temporally and spatially restricted expression patterns, and/or NR3 subunits A-B. The subunit NR2A, when deficient (such as in NR2A mutant mice), leads to decreased locomotor response to methamphetamine. Mice deficient in the NR2A subunit also show slower sensitisation to low doses of methamphetamine. This deficiency does not, however, affect their conditioned place preference (Miyamoto et al, 2004). Ethanol has been shown to inhibit the function of NMDA receptors (Hoffman et al, 1989; Lima-Landman et al, 1989; Lovinger et al, 1989; Lovinger et al, 1990a; Lovinger et al, 1990b), specifically the NMDA receptors with NR2B subunits expressed, while NR2C and NR3 subunits show a lower sensitivity to ethanol (Kuner et al, 1993; Masood et al, 1994). The route in which alcohol inhibits NMDA function is suggested to occur through a non-competitive mechanism that phosphorylates and internalises the NR2 subunits, thereby reducing long-term potentiation, and increasing long-term depression (Suvarna et al, 2005; Wang et al, 1997; Wirkner et al, 2000).

Known metabotropic glutamate receptors include mGluR1–mGluR8. Of these, mGluR5 is expressed in several areas of the reward system, including the VTA and the nucleus accumbens (Kenny et al, 2004). When activated by glutamate, mGluR5 couples to Gq and, through activation of phospholipase C, generates diacylglycerol and inositol 1,4,5-triphosphate. Mice lacking mGluR5 were found to fail in self-administration of cocaine (Chiamulera et al, 2001). In addition, an antagonist of mGluR5 (MPEP) disrupted cocaine's rewarding properties and reduced amphetamine's stimulant effects (Chiamulera et al, 2001; Mcgeehan et al, 2004). Thus far, the primary findings have been in psychostimulant drugs, as the mGluR5 antagonist (MPEP) does not impair place-conditioned preference to ethanol or nicotine (McGeehan et al, 2003). It has, however, been shown to reduce ethanol seeking and relapse behaviours (Backstrom et al, 2004).

Of great interest are the interactions of mGluR5 and mGluR1 with the scaffolding protein, Homer (Tu et al, 1998; Xiao et al, 1998). AMPA and NMDA receptors at the postsynaptic density have both, in turn, been linked to Homer 1 (Tu et al, 1999). These associations indicate that Homer exerts an influence on glutamatergic signalling pathways (Kammermeier et al, 2000). Homer1b/c isoform is reduced in the nucleus accumbens following cocaine withdrawal (Swanson et al, 2001), and Homer 2 has been shown to increase its sensitivity to cocaine and ethanol (Szumlinski et al, 2003).

Gamma-aminobutyric acid (GABA)

Gamma-aminobutyric acid (GABA) is the central nervous system's major inhibitory neurotransmitter. The exact role and involvement of GABA in substance abuse is still one of controversy and shows great complexity. The precursor to GABA is glutamate.

Glutamate is catalysed by glutamate decarboxylase with pyridoxal phosphate (vitamin B6). GABA neurons are predominantly interneurons (Kandel et al, 2000). There are three classes of GABAergic receptors: $GABA_A$, $GABA_B$ and $GABA_C$. $GABA_A$ and $GABA_C$ receptors are ionotropic receptors, and are thought of as fast-acting. Their activity leads to hyperpolarisation of the neuron, inhibiting excitation through opening Cl^- channels (Macdonald et al, 1994; Sieghart, 1995). $GABA_A$ receptor may also be activated by ethanol and several other drugs, including barbiturates and benzodiazepines (Johnston, 1996). Antagonists of $GABA_A$ (picrotoxin and bicuculline) decreased self-administration of cocaine and ethanol in rats (Petry, 1997; Valles et al, 2005). Also, direct injection of a $GABA_A$ antagonist (picrotoxin) into the VTA led to decreased ethanol consumption and increased the release of dopamine in the nucleus accumbens (Ikemoto et al, 1997). Furthermore, injection of $GABA_A$ agonist (muscimol) systemically, or directly, into the nucleus accumbens, decreased self-administration of ethanol (Petry, 1997). $GABA_B$ receptors are metabotropic, and their activity leads to activation of G-coupled proteins. When activated, these G-coupled proteins cause opening of transmembrane K^+ channels. They also suppress Ca^{++} channels, and reduce the activity of adenylate cyclase (Chen et al, 2005; Koob, 2004; Kuriyama et al, 2000). A $GABA_B$ receptor agonist (baclofen) has been found to attenuate self-administration of *d*-amphetamine, ethanol, and nicotine, in rats (Colombo et al, 2002; Di Ciano et al, 2003; Fattore et al, 2002; Paterson et al, 2004), and to reduce craving of these in addicted patients (Addolorato et al, 2002; Ling et al, 1998; Shoptaw et al, 2003). It has been suggested that $GABA_B$ agonists modulate the excitation of VTA dopaminergic neurons, thereby reducing the firing or tonic activity of the VTA (Lacey et al, 1988; Pinnock, 1984). GABA agonists and GABA antagonists are able to increase a brain stimulation reward process, which suggests a complex interaction between presynaptic and postsynaptic receptors. This accentuates the diverse nature of GABAergic interneuron function in different brain areas with addictive processes. As a target for genetic studies, the diversity of the GABAergic system is restrictive.

Polymorphisms within the $GABA_A$ receptor genes have been found to have an association with alcohol (Krystal et al, 2006) and illicit drug dependence. The *GABRA2* gene, which is located on chromosome 4, and which encodes the α-2 subunit of the $GABA_A$ receptor, has in particular been implicated on several occasions (Agrawal et al, 2006; Covault et al, 2004; Dick et al, 2006; Edenberg et al, 2004; Fehr et al, 2006; Lin et al, 2003; Soyka et al, 2008). However, these findings were not supported in subsequent studies involving other population groups (Lind et al, 2008; Onori et al, 2010). An additional study identified an association between SNPs within the gene encoding the $GABA_A$ γ-1 subunit (*GABRG1*) and alcohol dependence. These same authors also demonstrated that *GABRA2* and *GABRG1* are in linkage disequilibrium, which may account for the previous association of *GABRA2* with alcohol dependence. Thus, any previous associations implicating *GABRA2* in alcohol dependence may be due to the relationship with *GABRG1* and not due to a direct association with alcohol dependence (Covault et al, 2008). Individuals with particular *GABRG2* variants are at a higher risk of developing methamphetamine dependence (Nishiyama et al, 2005). In addition, *GABAB2* polymorphisms, which encode subunit 2 for the $GABA_B$ receptor, have been implicated in nicotine dependence (Beuten et al, 2005a).

Nicotine abuse

The molecular mechanisms that underlie nicotine addiction are not completely understood (Watkins et al, 2000). What is known is that nicotine binds to nicotinic acetylcholine receptors (nAChRs), which are expressed in both the peripheral and central nervous systems. Nicotine self-administration has been shown to enhance the release of dopamine in the nucleus accumbens, amygdala and prefrontal cortex (Wise, 2004). The $\alpha4\beta2$ nAChR subtype has been strongly implicated in nicotine addiction as: (1) an antagonist (DHβE), as well as a partial antagonist (SSR591813), to the $\alpha4\beta2$ nAChR subtype, decreased release of dopamine in the nucleus accumbens of the rat brain, and decreased self-administration of nicotine in rats (Cohen et al, 2003; Watkins et al, 1999); (2) genetic deletion of $\beta2$ subunit prevents nicotine self-administration in rats (Picciotto et al, 1998); (3) genetic deletion of $\alpha4$ subunit or $\beta2$ subunit shows decreased affinity in nicotine binding (Picciotto et al, 1995, 1998); (4) the increased expression of the $\alpha4\beta2$ nAChR subtype has been suggested to lead to nicotine addiction (Markou, 2008).

Catechol-O-methyl transferase (COMT) is involved in the degradation of dopamine within the prefrontal cortex (Wang et al, 2001).The Val158Met polymorphism within the *COMT* gene, located on chromosome 22, has demonstrated an association with nicotine dependence (Beuten et al, 2005b), as well as with vulnerability for polysubstance abuse (Vandenbergh et al, 1997). The Val/Val genotype has been shown to be significantly associated with smoking cessation (Omidvar et al, 2009). Individuals carrying the Val allele demonstrate a 40% increase in COMT activity in the brain as compared to those with the Met allele. Higher COMT activity is associated with lower levels of dopamine in the prefrontal cortex and, in turn, results in abnormal prefrontal cortical function (Chen et al, 2004). Twin studies have indicated that initial use of tobacco products has high heritability, approximately 75% (Maes et al, 2004). Continued smoking, which leads to nicotine dependence, has heritability of between 60% and 75% (Maes et al, 2004; True et al, 1999; Vink et al, 2005). This indicates that an individual's genetic background plays an important role in smoking addiction.

Cannabis abuse

Cannabis use and dependence has been shown to aggregate in families (Bierut et al, 1998; Brook et al, 1983; Brook et al, 1991; Johnson et al, 1984; Johnson et al, 2002; Merikangas et al, 1998). Use and dependence on cannabis has been related to genetic and environmental factors (Agrawal et al, 2004a,b; Kendler et al, 1998, 2003; Lynskey et al, 2003; Maes et al, 1999; Miles et al, 2001; Rhee et al, 2003; Tsuang et al, 1998; van den Bree et al, 1998). An association study linked cannabinoid-type1 (CB1) receptor expression and polysubstance abuse in humans (Zhang et al, 2004). Tetrahydrocannabiol is the main psychoactive ingredient of cannabis and acts at the CB1 receptor. The CB1 receptor is widely expressed throughout the peripheral and central nervous systems, including glia of the central nervous system. The majority of CB1 receptors are found presynpatically, and are coupled to inhibitory Gi/Go proteins. When activated, these proteins lead to inhibition of neurotransmitter release (Rada et al, 1998). CB1 receptors are not found on dopaminergic neurons. However, activation of CB1 receptors has been shown to enhance dopamine release. It has been suggested that CB1 receptors on GABAergic neurons

that innervate the VTA lead to disinhibition of VTA tonic activities, resulting in increased release of dopamine in the nucleus accumbens (Goodman, 2008).

Genome-wide association studies

Other genetic approaches are employed in the study of substance abuse. Genome-wide association studies (GWAS) use genetic variants, eg (SNPs) spread across the whole genome, to determine whether specific alleles may be associated with a phenotype (Hirschhorn et al, 2005). This approach utilises high-throughput genotyping techniques, such as microarray analysis, and allows the researcher to investigate most of the genome to determine the chromosomal regions or genes having an association with a disease (Baum et al, 2008). These studies are not hypothesis driven (Hirschhorn et al, 2005), and are thought to be useful for identifying variants which predispose to the development of complex disorders (Drgon et al, 2010).

Several GWAS have been carried out in relation to addictive substances. Two GWAS have identified genes involved in cell adhesion processes to be overrepresented for the general addiction phenotype (Drgon et al, 2010; Liu et al, 2006). GWAS for nicotine dependence have found the following genes to be highly associated: firstly, *Neurexin1* (*NRXN1*), which encodes a cell-surface protein, found mainly on neurons and functions in cell-cell interactions (Bierut et al, 2007); secondly, *interleukin 15* (*IL15*), a cytokine, which functions as a regulator of T and natural killer cell activation and proliferation (Liu et al, 2009). GWAS have also been used in an attempt to identify genomic regions associated with 'abstaining from smoking'. The genes identified as being 'quit-success genes' included those involved in biological processes such as cell adhesion, transcriptional and enzymatic functions, or DNA/RNA regulation. These authors also concluded that continued smoking cessation is a result of a polygenic effect (Uhl et al, 2008). Caporaso et al (2009) were unable to find any SNP that had significance for smoking behaviour in a group of European subjects (Caporaso et al, 2009).

However, many of the results that have been produced from GWAS have been unable to be replicated in independent studies. Due to phenotypic and locus heterogeneity, this may imply GWAS are not an ideal platform for identifying causative or associated variants of substance abuse disorders or psychiatric disorders. GWAS assumes the common disease common variant model (CDCV), which dictates that the disease phenotype is a result of multiple variants of small effect. However, these 'common' variants are undetectable by GWAS, which suggests that an alternate model be considered for complex disorders (Mitchell et al, 2009). Therefore, much of the current research on substance abuse has focused on gene-environment interactions, as well as epigenetic modifications.

Environmental effects on gene expression

The heritability for alcohol dependence, for example, is approximately 60%. This indicates that other factors, apart from genetics, are also involved in the development of addiction (Clarke et al, 2008). It has become quite evident that complex phenotypes, such as addiction, are not caused by a single gene effect, but are rather as a result of interactions between

numerous genetic factors and the environment (Li et al, 2009) (see Figure 6.4). The Virginia Twin Study demonstrated that, in early adolescence, the initial use of nicotine, alcohol and, cannabis is more strongly determined by familial and social factors rather than by genetic factors. However, with age, familial and social factors in substance abuse decline, so that by young to middle adulthood, genetic factors play a greater role. These results suggest that genetic factors override, or lead to, the persistence of substance use (Kendler et al, 2008). For example, the environment may prevent an individual from abusing a substance in the first instance, but may not be able to help a person who is already addicted (Rutter, 2006). However, this does not suggest that interactions between the environment and genetic factors do not increase the likelihood of developing an addiction (Mayer et al, 2005). Suggested behavioural characteristics, including impulsivity, risk-taking and novelty-seeking, are thought to lead to the initiation of substance use, and include the transition to addiction (Kreek et al, 2005). Some environmental risk factors include maternal stress, substance abuse during pregnancy, stressful life events, peer pressure and head injury (Clarke et al, 2008). In fact, some may argue that genetic susceptibility information may not have a significant impact on society. For example, a smoker may be less confident in his ability to quit if he is at a higher genetic risk to be a smoker (Humphreys, 2009). Nevertheless, several studies have investigated the effects of interactions between genes and the environment. Gene-environment interactions are defined as the effects of an environmental risk factor on an individual's health, based on that person's genotype at a particular locus (Caspi et al, 2006; Legrand et al, 2008). In other words, a genotypic effect may be attenuated or enhanced by certain environmental conditions (Legrand et al, 2008). The hypothalamic pituitary axis (HPA), which is involved in the body's stress response, has been investigated extensively in terms of substance abuse (Clarke et al, 2008). Stimulation or depression of the HPA is thought to have an influence on addiction (Kreek et al, 2005).

Childhood trauma has been suggested to be one of the major components, or risk factors, in the initiation and persistence of substance abuse (Dube et al, 2003). It has been proposed that the stress of 'childhood traumatic events' leads to a myriad of neurophysiological events that alter the development of the brain (Andersen, 2003; Teicher et al, 2002). It has further been suggested that there are windows of development during which the brain shows greater vulnerability to environmental factors that encourage addictions (Andersen et al, 2009). It has been observed that the environment has a greater role than genetics in influencing 'externalising behaviour' in adolescent males who reside in rural areas, as compared to their urban counterparts. This observation is based on the hypothesis that individuals living in urban areas have a greater personal choice, less influence from the environment and, therefore, a greater chance of genetics navigating their behaviour. Externalising behaviour is defined as 'unwillingness to conform to rules' and 'compulsive substance abuse' (Legrand et al, 2008).

The combination of the 3-repeat polymorphism in the promoter region of the *MAOA* gene and a dysfunctional environment, such as abuse or maltreatment, has been associated with alcohol-related problems in male adolescents (Nilsson et al, 2007). However, the longer 4-repeat allele has been associated with unfavourable environment and alcoholism in females (Nilsson et al, 2008). The 4-repeat allele leads to an increased level of *MAOA* activity, as compared to the 3-repeat allele (Deckert et al, 1999). The *5-HTTLPR* polymorphism

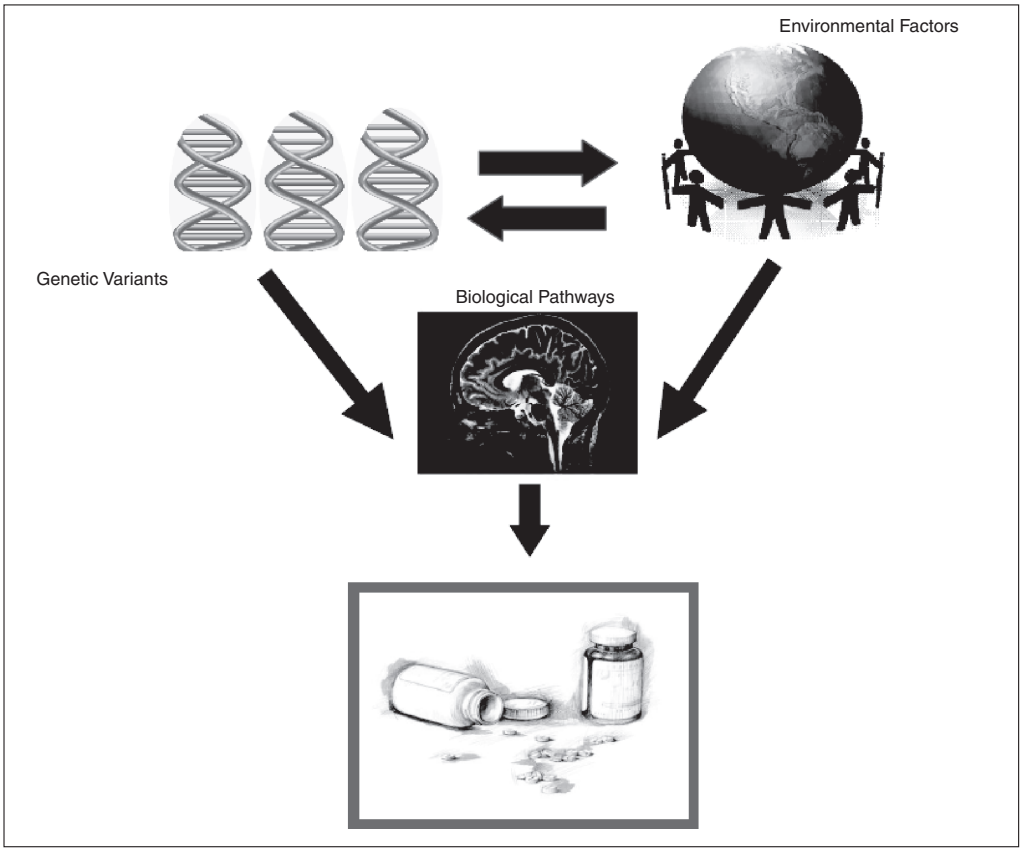

Figure 6.4: A diagrammatic representation of the interactions between genes, biological pathways and the environment leading to the substance abuse phenotype

has also been shown to have an interaction with adverse environmental conditions and alcoholism. A study conducted on rhesus macaques showed that those monkeys with the *L/S* genotype that were peer-reared instead of being reared maternally had greater ethanol consumption (Barr et al, 2004). Similarly, in humans, individuals with the heterozygous (*L/S*) genotype who were maltreated as children were more likely to have an early onset of alcohol use (Kaufman et al, 2007).

Epigenetics of substance abuse

The various functions and structural differences arising from different cell types in a multicellular organism are largely governed by differential gene expression in the cells. Epigenetics is the study of gene expression changes that are observed during development, and are mediated by stable alterations, which are subsequently inherited by daughter cells after mitosis. These alterations, which result from stochastic events, or environmental factors, are reversible. They do not result in changes to the actual DNA sequence (Jaenisch et al, 2003), but are governed rather by factors that are 'above the genome' (Renthal et al,

2008). DNA methylation and histone protein modification are two of the most commonly investigated mechanisms of epigenetics (Jaenisch et al, 2003).

Histones are a class of proteins involved in the packaging of the DNA sequence into a cell, and ultimately form the DNA-protein complex known as chromatin. The basic unit of chromatin is the nucleosome, which constitutes an octamer of core histone proteins surrounded by approximately 147bp of DNA. In its open conformation, chromatin is referred to as euchromatin, and in its more condensed, closed conformation, heterochromatin. Several types of covalent modifications are imposed on the amino acid residues within the 'tails' of histone proteins. Briefly, these include methylation, acetylation, phosphorylation, ribosylation, sumolation and ubiquitination. Acetylation is one of the commonly studied modification of histones, and it has been observed that hyperacetylation is associated with euchromatin, and hypoacteylation with hetrochromatin. The lysine and arginine amino acids of histones are often methylated, which may result in activation or silencing of a gene depending on which amino acid residue is de/methylated (Hake et al, 2004). It is thought that numerous post-translational modifications to chromatin are responsible for the final product of a particular gene (Renthal et al, 2008).

DNA methylation is predominantly found on the cytosine molecule of the cytosine-guanine dinucleotide repeats (referred to as CpG islands) of the DNA sequence, and results in the silencing of that particular section of the genome. During mammalian development, waves of methylation and demethylation occur at various time points, resulting in the expression of the appropriate genes (Jaenisch et al, 2003).

In 2009, Liu et al conducted an investigation to determine the effects of alcohol on methylation patterns during early embryonic neurulation. They found that cultured mouse embryos treated with alcohol had overall retarded growth, as well as developmental abnormalities of the heart, neural tube, brain vesicles, optical system and limb buds. Using a genome-wide platform, they observed changes in methylation patterns (both increased and decreased) in the embryos exposed to alcohol, and compared these to untreated control embryos. Altered methylation patterns were also correlated to severity of neural tube phenotype. Methylation changes were more prominent in embryos with open neural tubes than in those with closed neural tubes. Pathway analysis showed that the 147 genes that were hypermethylated in the alcohol-exposed group were genes involved in core embryonic developmental pathways (Liu et al, 2009).

Conclusion

There is high heritability in substance abuse. At present, a key neurotransmitter system for understanding normal reward, as well as the initial abuse and then the development of addiction to substances of abuse, is the dopaminergic system. Several other neurotransmitter systems may, however, also play a role in both normal reward and substance use disorders. An important goal of substance abuse research is to determine the genetic susceptibility to substance abuse. Work has focused on the genetics of relevant processes (eg, reward, stress), as well as on gene differences in substance abusers versus healthy controls. Recent advances in technology have allowed the interrogation of entire genomes, as well as the understanding of the complexities of epigenetic modifications. GWAS have identified promising regions

in the genome that may impart small effects towards the development of an addiction. However, GWAS do not show reproducibility. Studies such as those involving epigenetics are able to identify substance-induced gene expression changes, helping to understand the interplay between the environment and behavioural characteristics in the development of an addiction. Although the molecular basis and susceptibility to substance abuse has only begun to be unravelled, it is likely that further advances will be made in the not too distant future.

Acknowledgements

The authors wish to thank Dr Gemma Carvill, Ms Toni-Lee Sterley and Professor Rajkumar Ramesar for their editorial input to this chapter.

References

Addolorato, G., Caputo, F., Capristo, E., Domenicali, M., Bernardi, M., Janiri, L., Agabio, R., Colombo, G., Gessa, G.L. & Gasbarrini, G. (2002). Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. *Alcohol and Alcoholism*, 37(5):504–508.

Agrawal, A., Edenberg, H.J., Foroud, T., Bierut, L.J., Dunne, G., Hinrichs, A.L., Nurnberger, J.I., Crowe, R., Kuperman, S., Schuckit, M.A., Begleiter, H., Porjesz, B. & Dick, D.M. (2006). Association of GABRA2 with drug dependence in the collaborative study of the genetics of alcoholism sample. *Behavior Genetics*, 36(5):640–50.

Agrawal, A., Neale, M.C., Prescott, C.A. & Kendler, K.S. (2004a). Cannabis and other illicit drugs: comorbid use and abuse/dependence in males and females. *Behavior Genetics*, 34(3):217–28.

Agrawal, A., Neale, M.C., Prescott, C.A. & Kendler, K.S. (2004b). A twin study of early cannabis use and subsequent use and abuse/dependence of other illicit drugs. *Psychological Medicine*, 34(7):1227–37.

Andersen, S.L. (2003). Trajectories of brain development: point of vulnerability or window of opportunity? *Neuroscience and Biobehavioral Reviews*, 27(1–2):3–18.

Andersen, S.L.Teicher, M.H. (2009). Desperately driven and no brakes: developmental stress exposure and subsequent risk for substance abuse. *Neuroscience and Biobehavioral Reviews*, 33(4):516–24.

Ashworth-Preece, M.A., Chen, F., Jarrott, B. & Lawrence, A.J. (1999). Visualisation of AMPA binding sites in the brain stem of normotensive and hypertensive rats. *Brain Research*, 834(1–2):186–89.

Attwell, D. & Gibb, A. (2005). Neuroenergetics and the kinetic design of excitatory synapses. *Nature Reviews Neuroscience*, 6(11):841–49.

Backstrom, P., Bachteler, D., Koch, S., Hyytia, P. & Spanagel, R. (2004). mGluR5 antagonist MPEP reduces ethanol-seeking and relapse behavior. *Neuropsychopharmacology*, 29(5):921–28.

Barr, C.S., Newman, T.K., Lindell, S., Shannon, C., Champoux, M., Lesch, K.P., Suomi, S.J., Goldman, D. & Higley, J.D. (2004). Interaction between serotonin transporter

gene variation and rearing condition in alcohol preference and consumption in female primates. *Archives of General Psychiatry*, 61(11):1146–52.

Baum, A.E., Akula, N., Cabanero, M., Cardona, I., Corona, W., Klemens, B., Schulze, T.G., Cichon, S., Rietschel, M., Nothen, M.M., Georgi, A., Schumacher, J., Schwarz, M., Abou Jamra, R., Hofels, S., Propping, P., Satagopan, J., Detera-Wadleigh, S.D., Hardy, J. & McMahon, F.J. (2008). A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Molecular Psychiatry*, 13(2):197–207.

Beaulieu, J.M., Tirotta, E., Sotnikova, T.D., Masri, B., Salahpour, A., Gainetdinov, R.R., Borrelli, E. & Caron, M.G. (2007). Regulation of Akt signaling by D2 and D3 dopamine receptors in vivo. *The Journal of Neuroscience*, 27(4):881–85.

Beuten, J., Ma, J.Z., Payne, T.J., Dupont, R.T., Crews, K.M., Somes, G., Williams, N.J., Elston, R.C. & Li, M.D. (2005a). Single- and multilocus allelic variants within the GABA(B) receptor subunit 2 (GABAB2) gene are significantly associated with nicotine dependence. *American Journal of Human Genetics*, 76(5):859–64.

Beuten, J., Payne, T.J., Ma, J.Z. & Li, M.D. (2005b). Significant association of catechol-O-methyltransferase (COMT) haplotypes with nicotine dependence in male and female smokers of two ethnic populations. *Neuropsychopharmacology*, 31(3):675.

Bierut, L.J., Dinwiddie, S.H., Begleiter, H., Crowe, R.R., Hesselbrock, V., Nurnberger, J.I.,Jr, Porjesz, B., Schuckit, M.A. & Reich, T. (1998). Familial transmission of substance dependence: alcohol, marijuana, cocaine, and habitual smoking: a report from the Collaborative Study on the Genetics of Alcoholism. *Archives of General Psychiatry*,55(11):982–88.

Bierut, L.J., Madden, P.A., Breslau, N., Johnson, E.O., Hatsukami, D., Pomerleau, O.F., Swan, G.E., Rutter, J., Bertelsen, S., Fox, L., Fugman, D., Goate, A.M., Hinrichs, A.L., Konvicka, K., Martin, N.G., Montgomery, G.W., Saccone, N.L., Saccone, S.F., Wang, J.C., Chase, G.A., Rice, J.P. & Ballinger, D.G. (2007). Novel genes identified in a high-density genome wide association study for nicotine dependence. *Human Molecular Genetics*, 16(1):24–35.

Bisaga, A. & Popik, P. (2000). In search of a new pharmacological treatment for drug and alcohol addiction: N-methyl-D-aspartate (NMDA) antagonists. *Drug and Alcohol Dependence*, 59(1):1–15.

Blanc, G., Trovero, F., Vezina, P., Herve, D., Godeheu, A.M., Glowinski, J. & Tassin, J.P. (1994). Blockade of prefronto-cortical alpha 1-adrenergic receptors prevents locomotor hyperactivity induced by subcortical D-amphetamine injection. *The European Journal of Neuroscience*, 6(3):293–98.

Brook, J.S., Whiteman, M., Brook, D.W. & Gordon, A.S. (1991). Sibling influences on adolescent drug use: older brothers on younger brothers. *Journal of the American Academy of Child and Adolescent Psychiatry*, 30(6):958–66.

Brook, J.S., Whiteman, M., Gordon, A.S. & Brenden, C. (1983). Older brother's influence on younger sibling's drug use. *The Journal of Psychology*, 114(1st Half):83–90.

Budygin, E.A., Brodie, M.S., Sotnikova, T.D., Mateo, Y., John, C.E., Cyr, M., Gainetdinov, R.R. & Jones, S.R. (2004). Dissociation of rewarding and dopamine transporter-mediated properties of amphetamine. *Proceedings of the National Academy of Sciences*, 101(20):7781–86.

Caporaso, N., Gu, F., Chatterjee, N., Sheng-Chih, J., Yu, K., Yeager, M., Chen, C., Jacobs, K., Wheeler, W., Landi, M.T., Ziegler, R.G., Hunter, D.J., Chanock, S., Hankinson, S., Kraft, P. & Bergen, A.W. (2009). Genome-wide and candidate gene association study of cigarette smoking behaviors. *PloS One*, 4(2):e4653.

Carr, D.B. & Sesack, S.R. (2000). Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. *Journal of Neuroscience*, 20(10):3864–73.

Carta, A.R., Gerfen, C.R. & Steiner, H. (2000). Cocaine effects on gene regulation in the striatum and behavior: increased sensitivity in D3 dopamine receptor-deficient mice. *NeuroReport*, 11(11):2395–99.

Caspi, A. & Moffitt, T.E. (2006). Gene-environment interactions in psychiatry: joining forces with neuroscience. *Nature Reviews Neuroscience*, 7(7):583–90.

Chen, A.Q., Chen, X.C., Zhou, R.X. & Wang, W. (2008). Involvement of protein kinase C in NMDAR-dependent long-term potentiation in rat amygdala. *Acta Physiologica Sinica*, 60(6):737–42.

Chen, J., Lipska, B.K., Halim, N., Ma, Q.D., Matsumoto, M., Melhem, S., Kolachana, B.S., Hyde, T.M., Herman, M.M., Apud, J., Egan, M.F., Kleinman, J.E. & Weinberger, D.R. (2004). Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. *American Journal of Human Genetics*, 75(5):807–21.

Chen, K., Li, H.Z., Ye, N., Zhang, J. & Wang, J.J. (2005). Role of GABAB receptors in GABA and baclofen-induced inhibition of adult rat cerebellar interpositus nucleus neurons in vitro. *Brain Research Bulletin*, 67(4):310–18.

Chiamulera, C., Epping-Jordan, M.P., Zocchi, A., Marcon, C., Cottiny, C., Tacconi, S., Corsi, M., Orzi, F. & Conquet, F. (2001). Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. *Nature Neuroscience*, 4(9):873–74.

Churchill, L., Swanson, C.J., Urbina, M. & Kalivas, P.W. (1999). Repeated cocaine alters glutamate receptor subunit levels in the nucleus accumbens and ventral tegmental area of rats that develop behavioral sensitization. *Journal of Neurochemistry*, 72(6):2397–403.

Clarke, T.K., Treutlein, J., Zimmermann, U.S., Kiefer, F., Skowronek, M.H., Rietschel, M., Mann, K. & Schumann, G. (2008). HPA-axis activity in alcoholism: examples for a gene-environment interaction. *Addiction Biology*, 13(1):1–14.

Cohen, C., Bergis, O.E., Galli, F., Lochead, A.W., Jegham, S., Biton, B., Leonardon, J., Avenet, P., Sgard, F., Besnard, F., Graham, D., Coste, A., Oblin, A., Curet, O., Voltz, C., Gardes, A., Caille, D., Perrault, G., George, P., Soubrie, P. & Scatton, B. (2003). SSR591813, a novel selective and partial alpha4beta2 nicotinic receptor agonist with potential as an aid to smoking cessation. *The Journal of Pharmacology and Experimental Therapeutics*, 306(1):407–20.

Colombo, G., Serra, S., Brunetti, G., Atzori, G., Pani, M., Vacca, G., Addolorato, G., Froestl, W., Carai, M.A. & Gessa, G.L. (2002). The GABA(B) receptor agonists baclofen and CGP 44532 prevent acquisition of alcohol drinking behaviour in alcohol-preferring rats. *Alcohol and Alcoholism*, 37(5):499–503.

Comings, D.E. & Blum, K. (2000). Reward deficiency syndrome: genetic aspects of behavioral disorders. *Progress in Brain Research*, 126:325–41.

Comings, D.E., Muhleman, D., Ahn, C., Gysin, R. & Flanagan, S.D. (1994). The dopamine D2 receptor gene: a genetic risk factor in substance abuse. *Drug and Alcohol Dependence*, 34(3):175–80.

Connor, J.P., Young, R.M., Lawford, B.R., Ritchie, T.L. & Noble, E.P. (2002). D(2) dopamine receptor (DRD2) polymorphism is associated with severity of alcohol dependence. *European Psychiatry*, 17(1):17–23.

Covault, J., Gelernter, J., Hesselbrock, V., Nellissery, M. & Kranzler, H.R. (2004). Allelic and haplotypic association of GABRA2 with alcohol dependence. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 129B(1):104–109.

Covault, J., Gelernter, J., Jensen, K., Anton, R. & Kranzler, H.R. (2008). Markers in the 5'-region of GABRG1 associate to alcohol dependence and are in linkage disequilibrium with markers in the adjacent GABRA2 gene. *Neuropsychopharmacology*, 33(4):837–48.

Darracq, L., Blanc, G., Glowinski, J. & Tassin, J.P. (1998). Importance of the noradrenaline-dopamine coupling in the locomotor activating effects of D-amphetamine. *The Journal of Neuroscience*, 18(7):2729–39.

David, V., Segu, L., Buhot, M.C., Ichaye, M. & Cazala, P. (2004). Rewarding effects elicited by cocaine microinjections into the ventral tegmental area of C57BL/6 mice: involvement of dopamine D1 and serotonin1B receptors. *Psychopharmacology*, 174(3):367–75.

Davis, W.M., Smith, S.G. & Khalsa, J.H. (1975). Noradrenergic role in the self-administration of morphine or amphetamine. *Pharmacology, Biochemistry, and Behavior*, 3(3):477–84.

Deckert, J., Catalano, M., Syagailo, Y.V., Bosi, M., Okladnova, O., Di Bella, D., Nothen, M.M., Maffei, P., Franke, P., Fritze, J., Maier, W., Propping, P., Beckmann, H., Bellodi, L. & Lesch, K.P. (1999). Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. *Human Molecular Genetics*, 8(4):621–24.

Derkach, V.A., Oh, M.C., Guire, E.S. & Soderling, T.R. (2007). Regulatory mechanisms of AMPA receptors in synaptic plasticity. *Nature Reviews Neuroscience*, 8(2):101–13.

Devoto, P., Flore, G., Pani, L. & Gessa, G.L. (2001). Evidence for co-release of noradrenaline and dopamine from noradrenergic neurons in the cerebral cortex. *Molecular Psychiatry*, 6(6):657–64.

Devoto, P., Flore, G., Saba, P., Fa, M. & Gessa, G.L. (2005). Stimulation of the locus coeruleus elicits noradrenaline and dopamine release in the medial prefrontal and parietal cortex. *Journal of Neurochemistry*, 92(2):368–74.

Di Ciano, P. & Everitt, B.J. (2003). The GABA(B) receptor agonist baclofen attenuates cocaine- and heroin-seeking behavior by rats. *Neuropsychopharmacology*, 28(3):510–18.

Dick, D.M., Bierut, L., Hinrichs, A., Fox, L., Bucholz, K.K., Kramer, J., Kuperman, S., Hesselbrock, V., Schuckit, M., Almasy, L., Tischfield, J., Porjesz, B., Begleiter, H., Nurnberger, J., Jr, Xuei, X., Edenberg, H.J. & Foroud, T. (2006). The role of GABRA2 in risk for conduct disorder and alcohol and drug dependence across developmental stages. *Behavior Genetics*, 36(4):577–90.

Dick, D.M., Plunkett, J., Hamlin, D., Nurnberger, J., Jr, Kuperman, S., Schuckit, M., Hesselbrock, V., Edenberg, H. & Bierut, L. (2007). Association analyses of the serotonin transporter gene with lifetime depression and alcohol dependence in the Collaborative Study on the Genetics of Alcoholism (COGA) sample. *Psychiatric Genetics*, 17(1):35–38.

Drgon, T., Zhang, P.W., Johnson, C., Walther, D., Hess, J., Nino, M. & Uhl, G.R. (2010). Genome wide association for addiction: replicated results and comparisons of two analytic approaches. *PloS One*, 5(1):e8832.

Drouin, C., Darracq, L., Trovero, F., Blanc, G., Glowinski, J., Cotecchia, S. & Tassin, J.P. (2002). Alpha1b-adrenergic receptors control locomotor and rewarding effects of psychostimulants and opiates. *The Journal of Neuroscience*, 22(7):2873–84.

Dube, S.R., Felitti, V.J., Dong, M., Chapman, D.P., Giles, W.H. & Anda, R.F. (2003). Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. *Pediatrics*, 111(3):564–72.

Edenberg, H.J., Dick, D.M., Xuei, X., Tian, H., Almasy, L., Bauer, L.O., Crowe, R.R., Goate, A., Hesselbrock, V., Jones, K., Kwon, J., Li, T.K., Nurnberger, J.I., Jr, O'Connor, S.J., Reich, T., Rice, J., Schuckit, M.A., Porjesz, B., Foroud, T. & Begleiter, H. (2004). Variations in GABRA2, encoding the alpha 2 subunit of the GABA(A) receptor, are associated with alcohol dependence and with brain oscillations. *American Journal of Human Genetics*, 74(4):705–14.

Edenberg, H.J., Reynolds, J., Koller, D.L., Begleiter, H., Bucholz, K.K., Conneally, P.M., Crowe, R., Goate, A., Hesselbrock, V., Li, T.K., Nurnberger, J.I.,Jr, Porjesz, B., Reich, T., Rice, J.P., Schuckit, M., Tischfield, J.A. & Foroud, T. (1998). A family-based analysis of whether the functional promoter alleles of the serotonin transporter gene HTT affect the risk for alcohol dependence. *Alcoholism, Clinical and Experimental Research*, 22(5):1080–85.

Elliot, E.E., Sibley, D.R. & Katz, J.L. (2003). Locomotor and discriminative-stimulus effects of cocaine in dopamine D5 receptor knockout mice. *Psychopharmacology,* 169(2):161–68.

Fattore, L., Cossu, G., Martellotta, M.C. & Fratta, W. (2002). Baclofen antagonizes intravenous self-administration of nicotine in mice and rats. *Alcohol and Alcoholism*, 37(5):495–98.

Fehr, C., Sander, T., Tadic, A., Lenzen, K.P., Anghelescu, I., Klawe, C., Dahmen, N., Schmidt, L.G. & Szegedi, A. (2006). Confirmation of association of the GABRA2 gene with alcohol dependence by subtype-specific analysis. *Psychiatric Genetics*, 16(1):9–17.

Feinn, R., Nellissery, M. & Kranzler, H.R. (2005). Meta-analysis of the association of a functional serotonin transporter promoter polymorphism with alcohol dependence. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 133B(1):79–84.

Fon, E.A., Pothos, E.N., Sun, B.C., Killeen, N., Sulzer, D. & Edwards, R.H. (1997). Vesicular transport regulates monoamine storage and release but is not essential for amphetamine action. *Neuron*, 19(6):1271–83.

Ganong, W.F. 2001. *Review of Medical Physiology*. 20th edition. New York: McGraw-Hill Medical Publishing Division.

Gelernter, J., Kranzler, H.R., Satel, S.L. & Rao, P.A. (1994). Genetic association between dopamine transporter protein alleles and cocaine-induced paranoia. *Neuropsychopharmacology*, 11(3):195–200.

Gerra, G., Garofano, L., Santoro, G., Bosari, S., Pellegrini, C., Zaimovic, A., Moi, G., Bussandri, M., Moi, A., Brambilla, F. & Donnini, C. (2004). Association between

low-activity serotonin transporter genotype and heroin dependence: behavioral and personality correlates. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 126B(1):37–42.

Giros, B., Jaber, M., Jones, S.R., Wightman, R.M. & Caron, M.G. (1996). Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature*, 379(6566):606–12.

Glowinski, J. & Iversen, L. (1966). Regional studies of catecholamines in the rat brain. 3. Subcellullar distribution of endogenous and exogenous catecholamines in various brain regions. *Biochemical Pharmacology*, 15(7):977–87.

Goldman, D., Oroszi, G. & Ducci, F. (2006). The genetics of addictions: uncovering the genes. *Focus*, 284(5):2978.

Goodman, A. (2008). Neurobiology of addiction. An integrative review. *Biochemical Pharmacology*, 75(1):266–322.

Goodwin, J.S., Larson, G.A., Swant, J., Sen, N., Javitch, J.A., Zahniser, N.R., De Felice, L.J. & Khoshbouei, H. (2009). Amphetamine and methamphetamine differentially affect dopamine transporters in vitro and in vivo. *The Journal of Biological Chemistry*, 284(5):2978–89.

Gottfries, C.G., Oreland, L., Wiberg, A. & Winblad, B. (1975). Lowered monoamine oxidase activity in brains from alcoholic suicides. *Journal of Neurochemistry*, 25(5):667–73.

Grandy, D.K., Litt, M., Allen, L., Bunzow, J.R., Marchionni, M., Makam, H., Reed, L., Magenis, R.E. & Civelli, O. (1989). The human dopamine D2 receptor gene is located on chromosome 11 at q22-q23 and identifies a TaqI RFLP. *American Journal of Human Genetics*, 45(5):778–85.

Grenhoff, J.Svensson, T.H. (1993). Prazosin modulates the firing pattern of dopamine neurons in rat ventral tegmental area. *European Journal of Pharmacology*, 233(1): 79–84.

Gresch, P.J., Sved, A.F., Zigmond, M.J. & Finlay, J.M. (1995). Local influence of endogenous norepinephrine on extracellular dopamine in rat medial prefrontal cortex. *Journal of Neurochemistry*, 65(1):111–16.

Guan, X.M. & McBride, W.J. (1989). Serotonin microinfusion into the ventral tegmental area increases accumbens dopamine release. *Brain Research Bulletin*, 23(6):541–47.

Guardia, J., Catafau, A.M., Batlle, F., Martin, J.C., Segura, L., Gonzalvo, B., Prat, G., Carrio, I. & Casas, M. (2000). Striatal dopaminergic D(2) receptor density measured by [(123) I]iodobenzamide SPECT in the prediction of treatment outcome of alcohol-dependent patients. *The American Journal of Psychiatry*, 157(1):127–29.

Hake, S.B., Xiao, A. & Allis, C.D. (2004). Linking the epigenetic 'language' of covalent histone modifications to cancer. *British Journal of Cancer*, 90(4):761–69.

Heinz, A., Mann, K., Weinberger, D.R. & Goldman, D. (2001). Serotonergic dysfunction, negative mood states, and response to alcohol. *Alcoholism, Clinical and Experimental Research*, 25(4):487–95.

Hill, S.Y., Hoffman, E.K., Zezza, N., Thalamuthu, A., Weeks, D.E., Matthews, A.G. & Mukhopadhyay, I. (2008). Dopaminergic mutations: within-family association and linkage in multiplex alcohol dependence families. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 147B(4):517–26.

Hirschhorn, J.N. & Daly, M.J. (2005). Genome-wide association studies for common diseases and complex traits. *Nature Reviews Genetics*, 6(2):95–108.

Hoffman, P.L., Rabe, C.S., Moses, F. & Tabakoff, B. (1989). N-methyl-D-aspartate receptors and ethanol: inhibition of calcium flux and cyclic GMP production. *Journal of Neurochemistry*, 52(6):1937–40.

Huang, S.Y., Lin, W.W., Wan, F.J., Chang, A.J., Ko, H.C., Wang, T.J., Wu, P.L. & Lu, R.B. (2007). Monoamine oxidase-A polymorphisms might modify the association between the dopamine D2 receptor gene and alcohol dependence. *Journal of Psychiatry & Neuroscience*, 32(3):185–92.

Huang, S.Y., Lu, R.B., Ma, K.H., Shy, M.J. & Lin, W.W. (2008). Norepinephrine transporter polymorphisms T-182C and G1287A are not associated with alcohol dependence and its clinical subgroups. *Drug and Alcohol Dependence*, 92(1–3):20–26.

Humphreys, K. (2009). Searching where the light is worse: overemphasizing genes and underplaying environment in the quest to reduce substance misuse. *Clinical Pharmacology and Therapeutics*, 85(4):357–58.

Hyman, S.E. (2005). Addiction: a disease of learning and memory. *The American Journal of Psychiatry*, 162(8):1414–22.

Ikemoto, S., Kohl, R.R. & McBride, W.J. (1997). GABA(A) receptor blockade in the anterior ventral tegmental area increases extracellular levels of dopamine in the nucleus accumbens of rats. *Journal of Neurochemistry*, 69(1):137–43.

Jaenisch, R. & Bird, A. (2003). Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nature Genetics*, 33(Suppl):245–54.

Johanson, C.E., Frey, K.A., Lundahl, L.H., Keenan, P., Lockhart, N., Roll, J., Galloway, G.P., Koeppe, R.A., Kilbourn, M.R., Robbins, T. & Schuster, C.R. (2006). Cognitive function and nigrostriatal markers in abstinent methamphetamine abusers. *Psychopharmacology*,185(3):327–38.

Johnson, G.M., Shontz, F.C. & Locke, T.P. (1984). Relationships between adolescent drug use and parental drug behaviors. *Adolescence*, 19(74):295–99.

Johnson, J.G., Cohen, P., Gould, M.S., Kasen, S., Brown, J. & Brook, J.S. (2002). Childhood adversities, interpersonal difficulties, and risk for suicide attempts during late adolescence and early adulthood. *Archives of General Psychiatry*, 59(8):741–49.

Johnston, G.A. (1996). GABAA receptor pharmacology. *Pharmacology & Therapeutics*, 69(3):173–98.

Jones, S.R., Gainetdinov, R.R., Jaber, M., Giros, B., Wightman, R.M. & Caron, M.G. (1998). Profound neuronal plasticity in response to inactivation of the dopamine transporter. *Proceedings of the National Academy of Sciences*, 95(7):4029–34.

Jonsson, E.G., Nothen, M.M., Grunhage, F., Farde, L., Nakashima, Y., Propping, P. & Sedvall, G.C. (1999). Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Molecular Psychiatry*, 4(3):290–96.

Kalivas, P.W. & McFarland, K. (2003). Brain circuitry and the reinstatement of cocaine-seeking behavior. *Psychopharmacology*, 168(1–2):44–56.

Kalivas, P.W. & Stewart, J. (1991). Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Research. Brain Research Reviews*, 16(3):223–44.

Kammermeier, P.J., Xiao, B., Tu, J.C., Worley, P.F. & Ikeda, S.R. (2000). Homer proteins regulate coupling of group I metabotropic glutamate receptors to N-type calcium and M-type potassium channels. *The Journal of Neuroscience*, 20(19):7238–45.

Kandel, E.R., Schwartz, J.H. & Jessell, T.M. 2000. *Principles of Neural Science*. 4th edition. New York: McGraw-Hill Health Professions Division.

Katz, J.L., Chausmer, A.L., Elmer, G.I., Rubinstein, M., Low, M.J. & Grandy, D.K. (2003). Cocaine-induced locomotor activity and cocaine discrimination in dopamine D4 receptor mutant mice. *Psychopharmacology*, 170(1):108–14.

Kaufman, J., Yang, B.Z., Douglas-Palumberi, H., Crouse-Artus, M., Lipschitz, D., Krystal, J.H. & Gelernter, J. (2007). Genetic and environmental predictors of early alcohol use. *Biological Psychiatry*, 61(11):1228–34.

Kendler, K.S., Jacobson, K.C., Prescott, C.A. & Neale, M.C. (2003). Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *The American Journal of Psychiatry*, 160(4):687–95.

Kendler, K.S. & Prescott, C.A. (1998). Cannabis use, abuse, and dependence in a population-based sample of female twins. *The American Journal of Psychiatry*, 155(8):1016–22.

Kendler, K.S., Schmitt, E., Aggen, S.H. & Prescott, C.A. (2008). Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood. *Archives of General Psychiatry*, 65(6):674–82.

Kenny, P.J. & Markou, A. (2004). The ups and downs of addiction: role of metabotropic glutamate receptors. *Trends in Pharmacological Sciences*, 25(5):265–72.

Kohnke, M.D., Kolb, W., Lutz, U., Maurer, S. & Batra, A. (2006). The serotonin transporter promotor polymorphism 5-HTTLPR is not associated with alcoholism or severe forms of alcohol withdrawal in a German sample. *Psychiatric Genetics*, 16(6):227–28.

Konishi, T., Calvillo, M., Leng, A.S., Lin, K.M. & Wan, Y.J. (2004). Polymorphisms of the dopamine D2 receptor, serotonin transporter, and GABA(A) receptor beta(3) subunit genes and alcoholism in Mexican-Americans. *Alcohol*, 32(1):45–52.

Koob, G.F. (2004). A role for GABA mechanisms in the motivational effects of alcohol. *Biochemical Pharmacology*, 68(8):1515–25.

Kreek, M.J., Nielsen, D.A., Butelman, E.R. & LaForge, K.S. (2005). Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nature Neuroscience*, 8(11):1450–57.

Krystal, J.H., Staley, J., Mason, G., Petrakis, I.L., Kaufman, J., Harris, R.A., Gelernter, J. & Lappalainen, J. (2006). Gamma-aminobutyric acid type A receptors and alcoholism: intoxication, dependence, vulnerability, and treatment. *Archives of General Psychiatry*, 63(9):957–68.

Kuner, T., Schoepfer, R. & Korpi, E.R. (1993). Ethanol inhibits glutamate-induced currents in heteromeric NMDA receptor subtypes. *NeuroReport*, 5(3):297–300.

Kuriyama, K., Hirouchi, M. & Kimura, H. (2000). Neurochemical and molecular pharmacological aspects of the GABA(B) receptor. *Neurochemical Research*, 25(9–10): 1233–39.

Lacey, M.G., Mercuri, N.B. & North, R.A. (1988). On the potassium conductance increase activated by GABAB and dopamine D2 receptors in rat substantia nigra neurones. *The Journal of Physiology*, 401:437–53.

Laucht, M., Becker, K., Blomeyer, D. & Schmidt, M.H. (2007). Novelty seeking involved in mediating the association between the dopamine D4 receptor gene exon III polymorphism and heavy drinking in male adolescents: results from a high-risk community sample. *Biological Psychiatry*, 61(1):87–92.

Le, A.D., Harding, S., Juzytsch, W., Funk, D. & Shaham, Y. (2005). Role of alpha-2 adrenoceptors in stress-induced reinstatement of alcohol seeking and alcohol self-administration in rats. *Psychopharmacology*, 179(2):366–73.

Lee, B., Tiefenbacher, S., Platt, D.M. & Spealman, R.D. (2004). Pharmacological blockade of alpha2-adrenoceptors induces reinstatement of cocaine-seeking behavior in squirrel monkeys. *Neuropsychopharmacology*, 29(4):686–93.

Lee, H., Takamiya, K., Han, J., Man, H., Kim, C., Rumbaugh, G., Yu, S., Ding, L., He, C., Petralia, R.S., Wenthold, R.J., Gallagher, M. & Huganir, R.L. (2003). Phosphorylation of the AMPA Receptor GluR1 Subunit Is Required for Synaptic Plasticity and Retention of Spatial Memory. *Cell*, 112(5):631–43.

Legrand, L.N., Keyes, M., McGue, M., Iacono, W.G. & Krueger, R.F. (2008). Rural environments reduce the genetic influence on adolescent substance use and rule-breaking behavior. *Psychological Medicine*, 38(9):1341–50.

Lerman, C., Caporaso, N.E., Audrain, J., Main, D., Bowman, E.D., Lockshin, B., Boyd, N.R. & Shields, P.G. (1999). Evidence suggesting the role of specific genetic factors in cigarette smoking. *Health Psychology*, 18(1):14–20.

Lesch, K.P., Bengel, D., Heils, A., Sabol, S.Z., Greenberg, B.D., Petri, S., Benjamin, J., Muller, C.R., Hamer, D.H. & Murphy, D.L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, 274(5292):1527–31.

Lewis, R. (ed.) (2001). *Human Genetics: Concepts and Applications*. 4th edition. New York: McGraw-Hill.

Li, M.D. & Burmeister, M. (2009). New insights into the genetics of addiction. *Nature Reviews Genetics*, 10(4):225–31.

Li, T., Chen, C.K., Hu, X., Ball, D., Lin, S.K., Chen, W., Sham, P.C., Loh, E., Murray, R.M. & Collier, D.A. (2004). Association analysis of the DRD4 and COMT genes in methamphetamine abuse. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 129B(1):120–24.

Lichtermann, D., Hranilovic, D., Trixler, M., Franke, P., Jernej, B., Delmo, C.D., Knapp, M., Schwab, S.G., Maier, W. & Wildenauer, D.B. (2000). Support for allelic association of a polymorphic site in the promoter region of the serotonin transporter gene with risk for alcohol dependence. *The American Journal of Psychiatry*, 157(12): 2045–47.

Lima-Landman, M.T. & Albuquerque, E.X. (1989). Ethanol potentiates and blocks NMDA-activated single-channel currents in rat hippocampal pyramidal cells. *FEBS Letters*, 247(1):61–67.

Limosin, F., Gorwood, P., Loze, J.Y., Dubertret, C., Gouya, L., Deybach, J.C. & Ades, J. (2002). Male limited association of the dopamine receptor D2 gene TaqI a polymorphism and alcohol dependence. *American Journal of Medical Genetics*, 112(4): 343–46.

Lin, S.K., Chen, C.K., Ball, D., Liu, H.C. & Loh, E.W. (2003). Gender-specific contribution of the GABA(A) subunit genes on 5q33 in methamphetamine use disorder. *The Pharmacogenomics Journal*, 3(6):349–55.

Lind, P.A., Macgregor, S., Agrawal, A., Montgomery, G.W., Heath, A.C., Martin, N.G. & Whitfield, J.B. (2008). The role of GABRA2 in alcohol dependence, smoking, and illicit drug use in an Australian population sample. *Alcoholism, Clinical and Experimental Research*, 32(10):1721–31.

Ling, W., Shoptaw, S. & Majewska, D. (1998). Baclofen as a cocaine anti-craving medication: a preliminary clinical study. *Neuropsychopharmacology*, 18(5):403–404.

Linnoila, M., Virkkunen, M., Scheinin, M., Nuutila, A., Rimon, R. & Goodwin, F.K. (1983). Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. *Life Sciences*, 33(26):2609–14.

Liu, Q.R., Drgon, T., Johnson, C., Walther, D., Hess, J. & Uhl, G.R. (2006). Addiction molecular genetics: 639,401 SNP whole genome association identifies many 'cell adhesion' genes. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 141B(8):918–25.

Liu, Y., Balaraman, Y., Wang, G., Nephew, K.P. & Zhou, F.C. (2009). Alcohol exposure alters DNA methylation profiles in mouse embryos at early neurulation. *Epigenetics*, 4(7):500–11.

Lovinger, D.M., White, G. & Weight, F.F. (1989). Ethanol inhibits NMDA-activated ion current in hippocampal neurons. *Science*, 243(4899):1721–24.

Lovinger, D.M., White, G. & Weight, F.F. (1990a). Ethanol inhibition of neuronal glutamate receptor function. *Annals of Medicine*, 22(4):247–52.

Lovinger, D.M., White, G. & Weight, F.F. (1990b). NMDA receptor-mediated synaptic excitation selectively inhibited by ethanol in hippocampal slice from adult rat. *The Journal of Neuroscience*, 10(4):1372–79.

Lynskey, M.T., Heath, A.C., Bucholz, K.K., Slutske, W.S., Madden, P.A., Nelson, E.C., Statham, D.J. & Martin, N.G. (2003). Escalation of drug use in early-onset cannabis users vs co-twin controls. *The Journal of the American Medical Association*, 289(4):427–33.

Macdonald, R.L. & Olsen, R.W. (1994). GABAA receptor channels. *Annual Review of Neuroscience*, 17:569–602.

Maes, H.H., Sullivan, P.F., Bulik, C.M., Neale, M.C., Prescott, C.A., Eaves, L.J. & Kendler, K.S. (2004). A twin study of genetic and environmental influences on tobacco initiation, regular tobacco use and nicotine dependence. *Psychological Medicine*, 34(7):1251–61.

Maes, H.H., Woodard, C.E., Murrelle, L., Meyer, J.M., Silberg, J.L., Hewitt, J.K., Rutter, M., Simonoff, E., Pickles, A., Carbonneau, R., Neale, M.C. & Eaves, L.J. (1999). Tobacco, alcohol and drug use in eight- to sixteen-year-old twins: the Virginia Twin Study of Adolescent Behavioral Development. *Journal of Studies on Alcohol*, 60(3): 293–305.

Major, L.F., Goyer, P.F. & Murphy, D.L. (1981). Changes in platelet monoamine oxidase activity during abstinence. *Journal of Studies on Alcohol*, 42(11):1052–57.

Major, L.F. & Murphy, D.L. (1978). Platelet and plasma amine oxidase activity in alcoholic individuals. *The British Journal of Psychiatry*, 132:548–54.

Markou, A. (2008). Review. Neurobiology of nicotine dependence. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 363(1507):3159–68.

Masood, K., Wu, C., Brauneis, U. & Weight, F.F. (1994). Differential ethanol sensitivity of recombinant N-methyl-D-aspartate receptor subunits. *Molecular Pharmacology*, 45(2):324–29.

Mateo, Y., Budygin, E.A., John, C.E. & Jones, S.R. (2004). Role of serotonin in cocaine effects in mice with reduced dopamine transporter function. *Proceedings of the National Academy of Sciences*, 101(1):372–77.

Matsumoto, I., Wilce, P.A., Buckley, T., Dodd, P., Puzke, J., Spanagel, R., Zieglgansberger, W., Wolf, G., Leng, S., Rommelspacher, H., Finckh, U. & Schmidt, L.G. (2001). Ethanol and gene expression in brain. *Alcoholism, Clinical and Experimental Research*, 25(5 Suppl ISBRA):82S–6S.

Mayer, P. & Hollt, V. (2005). Genetic disposition to addictive disorders – current knowledge and future perspectives. *Current Opinion in Pharmacology*, 5(1):4–8.

McClung, C.A., Ulery, P.G., Perrotti, L.I., Zachariou, V., Berton, O. & Nestler, E.J. (2004). DeltaFosB: a molecular switch for long-term adaptation in the brain. *Brain Research. Molecular Brain Research*, 132(2):146–54.

McGeehan, A.J., Janak, P.H. & Olive, M.F. (2004). Effect of the mGluR5 antagonist 6-methyl-2-(phenylethynyl)pyridine (MPEP) on the acute locomotor stimulant properties of cocaine, D-amphetamine, and the dopamine reuptake inhibitor GBR12909 in mice. *Psychopharmacology*, 174(2):266–73.

McGeehan, A.J. & Olive, M.F. (2003). The mGluR5 antagonist MPEP reduces the conditioned rewarding effects of cocaine but not other drugs of abuse. *Synapse*, 47(3):240–42.

McHugh, R.K., Hofmann, S.G., Asnaani, A., Sawyer, A.T. & Otto, M.W. (2010). The serotonin transporter gene and risk for alcohol dependence: A meta-analytic review. *Drug and Alcohol Dependence*, 108(1–2):1–6.

Merikangas, K.R., Stolar, M., Stevens, D.E., Goulet, J., Preisig, M.A., Fenton, B., Zhang, H., O'Malley, S.S. & Rounsaville, B.J. (1998). Familial transmission of substance use disorders. *Archives of General Psychiatry*, 55(11):973–79.

Miles, D.R., Van den Bree, M.B., Gupman, A.E., Newlin, D.B., Glantz, M.D. & Pickens, R.W. (2001). A twin study on sensation seeking, risk taking behavior and marijuana use. *Drug and Alcohol Dependence*, 62(1):57–68.

Mitchell, K.J. & Porteous, D.J. (2009). GWAS for psychiatric disease: is the framework built on a solid foundation? *Molecular Psychiatry*, 14(8):740–41.

Miyamoto, Y., Yamada, K., Nagai, T., Mori, H., Mishina, M., Furukawa, H., Noda, Y. & Nabeshima, T. (2004). Behavioural adaptations to addictive drugs in mice lacking the NMDA receptor epsilon1 subunit. *The European Journal of Neuroscience*, 19(1):151–58.

Munafo, M.R., Lingford-Hughes, A.R., Johnstone, E.C. & Walton, R.T. (2005). Association between the serotonin transporter gene and alcohol consumption in social drinkers. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 135B(1):10–14.

Nestler, E.J. (2002). From neurobiology to treatment: progress against addiction. *Nature Neuroscience*, 5(Suppl.):1076–79.

Nilsson, K.W., Sjoberg, R.L., Wargelius, H.L., Leppert, J., Lindstrom, L. & Oreland, L. (2007). The monoamine oxidase A (MAO-A) gene, family function and maltreatment

as predictors of destructive behaviour during male adolescent alcohol consumption. *Addiction*, 102(3):389–98.

Nilsson, K.W., Wargelius, H.L., Sjoberg, R.L., Leppert, J. & Oreland, L. (2008). The *MAO-A* gene, platelet *MAO-B* activity and psychosocial environment in adolescent female alcohol-related problem behaviour. *Drug and Alcohol Dependence*, 93(1-2):51–62.

Nishiyama, T., Ikeda, M., Iwata, N., Suzuki, T., Kitajima, T., Yamanouchi, Y., Sekine, Y., Iyo, M., Harano, M., Komiyama, T., Yamada, M., Sora, I., Ujike, H., Inada, T., Furukawa, T. & Ozaki, N. (2005). Haplotype association between GABAA receptor gamma2 subunit gene (GABRG2) and methamphetamine use disorder. *The Pharmacogenomics Journal*, 5(2):89–95.

Noble, E.P. (2003). D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 116B(1):103–25.

Noble, E.P., Blum, K., Khalsa, M.E., Ritchie, T., Montgomery, A., Wood, R.C., Fitch, R.J., Ozkaragoz, T., Sheridan, P.J. & Anglin, M.D. (1993). Allelic association of the D2 dopamine receptor gene with cocaine dependence. *Drug and Alcohol Dependence*, 33(3):271–85.

Noble, E.P., Blum, K., Ritchie, T., Montgomery, A. & Sheridan, P.J. (1991). Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Archives of General Psychiatry*, 48(7):648–54.

Noble, E.P., Gottschalk, L.A., Fallon, J.H., Ritchie, T.L. & Wu, J.C. (1997). D2 dopamine receptor polymorphism and brain regional glucose metabolism. *American Journal of Medical Genetics*, 74(2):162–66.

O'Hara, B.F., Smith, S.S., Bird, G., Persico, A.M., Suarez, B.K., Cutting, G.R. & Uhl, G.R. (1993). Dopamine D2 receptor RFLPs, haplotypes and their association with substance use in black and Caucasian research volunteers. *Human Heredity*, 43(4):209–18.

Omidvar, M., Stolk, L., Uitterlinden, A.G., Hofman, A., Van Duijn, C.M. & Tiemeier, H. (2009). The effect of catechol-O-methyltransferase Met/Val functional polymorphism on smoking cessation: retrospective and prospective analyses in a cohort study. *Pharmacogenetics and Genomics*, 19(1):45–51.

Onori, N., Turchi, C., Solito, G., Gesuita, R., Buscemi, L. & Tagliabracci, A. (2010). GABRA2 and alcohol use disorders: no evidence of an association in an Italian case-control study. *Alcoholism, Clinical and Experimental Research,* 34(4):659–68.

Oreland, L., Wiberg, A., Winblad, B., Fowler, C.J., Gottfries, C.G. & Kiianmaa, K. (1983). The activity of monoamine oxidase -A and -B in brains from chronic alcoholics. *Journal of Neural Transmission*, 56(1):73–83.

Ortiz, J., DeCaprio, J.L., Kosten, T.A. & Nestler, E.J. (1995). Strain-selective effects of corticosterone on locomotor sensitization to cocaine and on levels of tyrosine hydroxylase and glucocorticoid receptor in the ventral tegmental area. *Neuroscience*, 67(2):383–97.

Paoletti, P. & Neyton, J. (2007). NMDA receptor subunits: function and pharmacology. *Current Opinion in Pharmacology*, 7(1):39–47.

Paterson, N.E., Froestl, W. & Markou, A. (2004). The GABAB receptor agonists baclofen and CGP44532 decreased nicotine self-administration in the rat. *Psychopharmacology*, 172(2):179–86.

Peakman, M.C., Colby, C., Perrotti, L.I., Tekumalla, P., Carle, T., Ulery, P., Chao, J., Duman, C., Steffen, C., Monteggia, L., Allen, M.R., Stock, J.L., Duman, R.S., McNeish, J.D., Barrot, M., Self, D.W., Nestler, E.J. & Schaeffer, E. (2003). Inducible, brain region-specific expression of a dominant negative mutant of c-Jun in transgenic mice decreases sensitivity to cocaine. *Brain Research*, 970(1–2):73–86.

Persico, A.M., Bird, G., Gabbay, F.H. & Uhl, G.R. (1996). D2 dopamine receptor gene TaqI A1 and B1 restriction fragment length polymorphisms: enhanced frequencies in psychostimulant-preferring polysubstance abusers. *Biological Psychiatry*, 40(8):776–84.

Pessia, M., Jiang, Z.G., North, R.A. & Johnson, S.W. (1994). Actions of 5-hydroxytryptamine on ventral tegmental area neurons of the rat in vitro. *Brain Research*, 654(2):324–30.

Petry, N.M. (1997). Benzodiazepine-GABA modulation of concurrent ethanol and sucrose reinforcement in the rat. *Experimental and Clinical Psychopharmacology*, 5(3):183–94.

Picciotto, M.R., Zoli, M., Lena, C., Bessis, A., Lallemand, Y., Le Novere, N., Vincent, P., Pich, E.M., Brulet, P. & Changeux, J.P. (1995). Abnormal avoidance learning in mice lacking functional high-affinity nicotine receptor in the brain. *Nature*, 374(6517):65–67.

Picciotto, M.R., Zoli, M., Rimondini, R., Lena, C., Marubio, L.M., Pich, E.M., Fuxe, K. & Changeux, J.P. (1998). Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. *Nature*, 391(6663):173–77.

Pinnock, R.D. (1984). Hyperpolarizing action of baclofen on neurons in the rat substantia nigra slice. *Brain Research*, 322(2):337–40.

Pohjalainen, T., Rinne, J.O., Nagren, K., Lehikoinen, P., Anttila, K., Syvalahti, E.K. & Hietala, J. (1998). The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. *Molecular Psychiatry*, 3(3):256–60.

Ponce, G., Hoenicka, J., Jimenez-Arriero, M.A., Rodriguez-Jimenez, R., Aragues, M., Martin-Sune, N., Huertas, E. & Palomo, T. (2008). DRD2 and ANKK1 genotype in alcohol-dependent patients with psychopathic traits: association and interaction study. *The British Journal of Psychiatry*, 193(2):121–25.

Rada, P., Mark, G.P. & Hoebel, B.G. (1998). Galanin in the hypothalamus raises dopamine and lowers acetylcholine release in the nucleus accumbens: a possible mechanism for hypothalamic initiation of feeding behavior. *Brain Research*, 798(1–2):1–6.

Rasmussen, H., Bagger, Y., Tanko, L.B., Christiansen, C. & Werge, T. (2008). Lack of association of the serotonin transporter gene promotor region polymorphism, 5-HTTLPR, including rs25531 with cigarette smoking and alcohol consumption. Part B neuropsychiatric genetics. *American Journal of Medical Genetics*, 150B(4):575–80.

Renthal, W. & Nestler, E.J. (2008). Epigenetic mechanisms in drug addiction. *Trends in Molecular Medicine*, 14(8):341–50.

Rhee, S.H., Hewitt, J.K., Young, S.E., Corley, R.P., Crowley, T.J. & Stallings, M.C. (2003). Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Archives of General Psychiatry*, 60(12):1256–64.

Ritz, M.C., Lamb, R.J., Goldberg, S.R. & Kuhar, M.J. (1987). Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science*, 237(4819):1219–23.

Robinson, T.E. & Becker, J.B. (1986). Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Research*, 396(2):157–98.

Rocha, B.A. (2003). Stimulant and reinforcing effects of cocaine in monoamine transporter knockout mice. *European Journal of Pharmacology*, 479(1–3):107–15.

Rocha, B.A., Fumagalli, F., Gainetdinov, R.R., Jones, S.R., Ator, R., Giros, B., Miller, G.W. & Caron, M.G. (1998). Cocaine self-administration in dopamine-transporter knockout mice. *Nature Neuroscience*, 1(2):132–37.

Rothman, R.B. & Baumann, M.H. (2006). Balance between dopamine and serotonin release modulates behavioral effects of amphetamine-type drugs. *Annals of the New York Academy of Sciences*, 1074:245–60.

Rothman, R.B., Baumann, M.H., Dersch, C.M., Romero, D.V., Rice, K.C., Carroll, F.I. & Partilla, J.S. (2001). Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*, 39(1):32–41.

Rothman, R.B., Blough, B.E. & Baumann, M.H. (2008). Dopamine/serotonin releasers as medications for stimulant addictions. *Progress in Brain Research*, 172:385–406.

Rubinstein, M., Phillips, T.J., Bunzow, J.R., Falzone, T.L., Dziewczapolski, G., Zhang, G., Fang, Y., Larson, J.L., McDougall, J.A., Chester, J.A., Saez, C., Pugsley, T.A., Gershanik, O., Low, M.J. & Grandy, D.K. (1997). Mice lacking dopamine D4 receptors are supersensitive to ethanol, cocaine, and methamphetamine. *Cell*, 90(6):991–1001.

Rusakov, D.A.Kullmann, D.M. (1998). Extrasynaptic glutamate diffusion in the hippocampus: ultrastructural constraints, uptake, and receptor activation. *The Journal of Neuroscience*, 18(9):3158–70.

Rutter, J.L. (2006). Symbiotic relationship of pharmacogenetics and drugs of abuse. *The AAPS Journal*, 8(1):E174–84.

Sabol, S.Z., Nelson, M.L., Fisher, C., Gunzerath, L., Brody, C.L., Hu, S., Sirota, L.A., Marcus, S.E., Greenberg, B.D., Lucas, F.R.,4th, Benjamin, J., Murphy, D.L. & Hamer, D.H. (1999). A genetic association for cigarette smoking behavior. *Health Psychology*, 18(1):7–13.

Sander, T., Harms, H., Lesch, K.P., Dufeu, P., Kuhn, S., Hoehe, M., Rommelspacher, H. & Schmidt, L.G. (1997). Association analysis of a regulatory variation of the serotonin transporter gene with severe alcohol dependence. *Alcoholism, Clinical and Experimental Research*, 21(8):1356–59.

Sekine, Y., Ouchi, Y., Takei, N., Yoshikawa, E., Nakamura, K., Futatsubashi, M., Okada, H., Minabe, Y., Suzuki, K., Iwata, Y., Tsuchiya, K.J., Tsukada, H., Iyo, M. & Mori, N. (2006). Brain serotonin transporter density and aggression in abstinent methamphetamine abusers. *Archives of General Psychiatry*, 63(1):90–100.

Shoptaw, S., Yang, X., Rotheram-Fuller, E.J., Hsieh, Y.C., Kintaudi, P.C., Charuvastra, V.C. & Ling, W. (2003). Randomized placebo-controlled trial of baclofen for cocaine dependence: preliminary effects for individuals with chronic patterns of cocaine use. *The Journal of Clinical Psychiatry*, 64(12):1440–48.

Sieghart, W. (1995). Structure and pharmacology of gamma-aminobutyric acidA receptor subtypes. *Pharmacological Reviews*, 47(2):181–234.

Smith, L., Watson, M., Gates, S., Ball, D. & Foxcroft, D. (2008). Meta-analysis of the association of the Taq1A polymorphism with the risk of alcohol dependency: a HuGE gene-disease association review. *American Journal of Epidemiology*, 167(2):125–38.

Snyder, S.H. & Coyle, J.T. (1969). Regional differences in H3-norepinephrine and H3-dopamine uptake into rat brain homogenates. *The Journal of Pharmacology and Experimental Therapeutics*, 165(1):78–86.

Sora, I., Wichems, C., Takahashi, N., Li, X.F., Zeng, Z., Revay, R., Lesch, K.P., Murphy, D.L. & Uhl, G.R. (1998). Cocaine reward models: conditioned place preference can be established in dopamine- and in serotonin-transporter knockout mice. *Proceedings of the National Academy of Sciences*, 95(13):7699–704.

Soyka, M., Preuss, U.W., Hesselbrock, V., Zill, P., Koller, G. & Bondy, B. (2008). GABA-A2 receptor subunit gene (GABRA2) polymorphisms and risk for alcohol dependence. *Journal of Psychiatric Research*, 42(3):184–91.

Sutton, M.A., Schmidt, E.F., Choi, K.H., Schad, C.A., Whisler, K., Simmons, D., Karanian, D.A., Monteggia, L.M., Neve, R.L. & Self, D.W. (2003). Extinction-induced upregulation in AMPA receptors reduces cocaine-seeking behaviour. *Nature*, 421(6918):70–75.

Suvarna, N., Borgland, S.L., Wang, J., Phamluong, K., Auberson, Y.P., Bonci, A. & Ron, D. (2005). Ethanol alters trafficking and functional N-methyl-D-aspartate receptor NR2 subunit ratio via H-Ras. *The Journal of Biological Chemistry*, 280(36):31450–59.

Swanson, C.J., Baker, D.A., Carson, D., Worley, P.F. & Kalivas, P.W. (2001). Repeated cocaine administration attenuates group I metabotropic glutamate receptor-mediated glutamate release and behavioral activation: a potential role for Homer. *The Journal of Neuroscience*, 21(22):9043–52.

Szumlinski, K.K., Toda, S., Middaugh, L.D., Worley, P.F. & Kalivas, P.W. (2003). Evidence for a relationship between Group 1 mGluR hypofunction and increased cocaine and ethanol sensitivity in Homer2 null mutant mice. *Annals of the New York Academy of Sciences*, 1003:468–71.

Takahashi, N., Miner, L.L., Sora, I., Ujike, H., Revay, R.S., Kostic, V., Jackson-Lewis, V., Przedborski, S. & Uhl, G.R. (1997). VMAT2 knockout mice: heterozygotes display reduced amphetamine-conditioned reward, enhanced amphetamine locomotion, and enhanced MPTP toxicity. *Proceedings of the National Academy of Sciences*, 94(18):9938–43.

Takahashi, T. (2005). Postsynaptic receptor mechanisms underlying developmental speeding of synaptic transmission. *Neuroscience Research*, 53(3):229–40.

Teicher, M.H., Andersen, S.L., Polcari, A., Anderson, C.M. & Navalta, C.P. (2002). Developmental neurobiology of childhood stress and trauma. *The Psychiatric Clinics of North America*, 25(2):397–426, vii–viii.

True, W.R., Xian, H., Scherrer, J.F., Madden, P.A., Bucholz, K.K., Heath, A.C., Eisen, S.A., Lyons, M.J., Goldberg, J. & Tsuang, M. (1999). Common genetic vulnerability for nicotine and alcohol dependence in men. *Archives of General Psychiatry*, 56(7):655–61

Tsuang, M.T., Lyons, M.J., Meyer, J.M., Doyle, T., Eisen, S.A., Goldberg, J., True, W., Lin, N., Toomey, R. & Eaves, L. (1998). Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Archives of General Psychiatry*, 55(11):967–72.

Tu, J.C., Xiao, B., Naisbitt, S., Yuan, J.P., Petralia, R.S., Brakeman, P., Doan, A., Aakalu, V.K., Lanahan, A.A., Sheng, M. & Worley, P.F. (1999). Coupling of mGluR/Homer and PSD-95 complexes by the Shank family of postsynaptic density proteins. *Neuron*, 23(3):583–92.

Tu, J.C., Xiao, B., Yuan, J.P., Lanahan, A.A., Leoffert, K., Li, M., Linden, D.J. & Worley, P.F. (1998). Homer binds a novel proline-rich motif and links group 1 metabotropic glutamate receptors with IP3 receptors. *Neuron*, 21(4):717–26.

Tully, T., Bourtchouladze, R., Scott, R. & Tallman, J. (2003). Targeting the CREB pathway for memory enhancers. *Nature Reviews, Drug Discovery*, 2(4):267–77.

Uhl, G.R., Liu, Q.R., Drgon, T., Johnson, C., Walther, D., Rose, J.E., David, S.P., Niaura, R. & Lerman, C. (2008). Molecular genetics of successful smoking cessation: convergent genome-wide association study results. *Archives of General Psychiatry*, 65(6):683–93.

Ujike, H., Katsu, T., Okahisa, Y., Takaki, M., Kodama, M., Inada, T., Uchimura, N., Yamada, M., Iwata, N., Sora, I., Iyo, M., Ozaki, N. & Kuroda, S. (2009). Genetic variants of D2 but not D3 or D4 dopamine receptor gene are associated with rapid onset and poor prognosis of methamphetamine psychosis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 33(4):625–29.

Ungless, M.A., Whistler, J.L., Malenka, R.C. & Bonci, A. (2001). Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature*, 411(6837): 583–87.

Valles, R., Rocha, A., Cardon, A., Bratton, G.R. & Nation, J.R. (2005). The effects of the GABAA antagonist bicuculline on cocaine self-administration in rats exposed to lead during gestation/lactation. *Pharmacology, Biochemistry, and Behavior*, 80(4):611–19.

Van den Bree, M.B., Johnson, E.O., Neale, M.C. & Pickens, R.W. (1998). Genetic and environmental influences on drug use and abuse/dependence in male and female twins. *Drug and Alcohol Dependence*, 52(3):231–41.

Vandenbergh, D.J., Rodriguez, L.A., Hivert, E., Schiller, J.H., Villareal, G., Pugh, E.W., Lachman, H. & Uhl, G.R. (2000). Long forms of the dopamine receptor (DRD4) gene VNTR are more prevalent in substance abusers: no interaction with functional alleles of the catechol-o-methyltransferase (COMT) gene. *American Journal of Medical Genetics*, 96(5):678–83.

Vandenbergh, D.J., Rodriguez, L.A., Miller, I.T., Uhl, G.R. & Lachman, H.M. (1997). High-activity catechol-O-methyltransferase allele is more prevalent in polysubstance abusers. *American Journal of Medical Genetics*, 74(4):439–42.

Vekovischeva, O.Y., Zamanillo, D., Echenko, O., Seppala, T., Uusi-Oukari, M., Honkanen, A., Seeburg, P.H., Sprengel, R. & Korpi, E.R. (2001). Morphine-induced dependence and sensitization are altered in mice deficient in AMPA-type glutamate receptor-A subunits. *The Journal of Neuroscience*, 21(12):4451–59.

Vink, J.M., Willemsen, G. & Boomsma, D.I. (2005). Heritability of smoking initiation and nicotine dependence. *Behavior Genetics*, 35(4):397–406.

Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Ding, Y.S., Sedler, M., Logan, J., Franceschi, D., Gatley, J., Hitzemann, R., Gifford, A., Wong, C. & Pappas, N. (2001). Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *The American Journal of Psychiatry*, 158(12):2015–21.

Volkow, N.D., Fowler, J.S. & Wang, G.J. (2004a). The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology*, 47(Suppl. 1):3–13.

Volkow, N.D., Fowler, J.S., Wang, G.J. & Swanson, J.M. (2004b). Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Molecular Psychiatry*, 9(6):557–69.

Walters, C.L., Kuo, Y.C. & Blendy, J.A. (2003). Differential distribution of CREB in the mesolimbic dopamine reward pathway. *Journal of Neurochemistry*, 87(5):1237–44.

Wang, Y., Berndt, T.J., Gross, J.M., Peterson, M.A., So, M.J. & Knox, F.G. (2001). Effect of inhibition of MAO and COMT on intrarenal dopamine and serotonin and on renal function. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, 280(1):R248–54.

Wang, Y.M., Gainetdinov, R.R., Fumagalli, F., Xu, F., Jones, S.R., Bock, C.B., Miller, G.W., Wightman, R.M. & Caron, M.G. (1997). Knockout of the vesicular monoamine transporter 2 gene results in neonatal death and supersensitivity to cocaine and amphetamine. *Neuron*, 19(6):1285–96.

Watkins, S.S., Epping-Jordan, M.P., Koob, G.F. & Markou, A. (1999). Blockade of nicotine self-administration with nicotinic antagonists in rats. *Pharmacology, Biochemistry, and Behavior*, 62(4):743–51.

Watkins, S.S., Koob, G.F. & Markou, A. (2000). Neural mechanisms underlying nicotine addiction: acute positive reinforcement and withdrawal. *Nicotine & Tobacco Research*, 2(1):19–37.

Wiberg, A. (1979). Increase in platelet monoamine oxidase activity during controlled abstinence after alcohol abuse. *Medical Biology*, 57(2):133–34.

Willis-Owen, S.A., Turri, M.G., Munafo, M.R., Surtees, P.G., Wainwright, N.W., Brixey, R.D. & Flint, J. (2005). The serotonin transporter length polymorphism, neuroticism, and depression: a comprehensive assessment of association. *Biological Psychiatry*, 58(6):451–56.

Wirkner, K., Eberts, C., Poelchen, W., Allgaier, C. & Illes, P. (2000). Mechanism of inhibition by ethanol of NMDA and AMPA receptor channel functions in cultured rat cortical neurons. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 362(6):568–76.

Wise, R.A. (2004). Dopamine, learning and motivation. *Nature Reviews Neuroscience*, 5(6):483–94.

Wise, R.A. (2005). Forebrain substrates of reward and motivation. *The Journal of Comparative Neurology*, 493(1):115–21.

Wise, R.A. (2009). Roles for nigrostriatal – not just mesocorticolimbic – dopamine in reward and addiction. *Trends in Neurosciences*, 32(10):517–24.

Wolf, M.E., Sun, X., Mangiavacchi, S. & Chao, S.Z. (2004). Psychomotor stimulants and neuronal plasticity. *Neuropharmacology*, 47(Suppl. 1):61–79.

Xiao, B., Tu, J.C., Petralia, R.S., Yuan, J.P., Doan, A., Breder, C.D., Ruggiero, A., Lanahan, A.A., Wenthold, R.J. & Worley, P.F. (1998). Homer regulates the association of group 1 metabotropic glutamate receptors with multivalent complexes of homer-related, synaptic proteins. *Neuron*, 21(4):707–16.

Xu, M., Guo, Y., Vorhees, C.V. & Zhang, J. (2000). Behavioral responses to cocaine and amphetamine administration in mice lacking the dopamine D1 receptor. *Brain Research*, 852(1):198–207.

Xu, M., Hu, X.T., Cooper, D.C., Moratalla, R., Graybiel, A.M., White, F.J. & Tonegawa, S. (1994). Elimination of cocaine-induced hyperactivity and dopamine-mediated neurophysiological effects in dopamine D1 receptor mutant mice. *Cell*, 79(6):945–55.

Xu, M., Koeltzow, T.E., Santiago, G.T., Moratalla, R., Cooper, D.C., Hu, X.T., White, N.M., Graybiel, A.M., White, F.J. & Tonegawa, S. (1997). Dopamine D3 receptor mutant mice exhibit increased behavioral sensitivity to concurrent stimulation of D1 and D2 receptors. *Neuron*, 19(4):837–48.

Yamamoto, B.K. & Novotney, S. (1998). Regulation of extracellular dopamine by the norepinephrine transporter. *Journal of Neurochemistry*, 71(1):274–80.

Yan, Q.S., Zheng, S.Z. & Yan, S.E. (2004). Involvement of 5-HT1B receptors within the ventral tegmental area in regulation of mesolimbic dopaminergic neuronal activity via GABA mechanisms: a study with dual-probe microdialysis. *Brain Research*, 1021(1):82–91.

Zhang, P.W., Ishiguro, H., Ohtsuki, T., Hess, J., Carillo, F., Walther, D., Onaivi, E.S., Arinami, T. & Uhl, G.R. (2004). Human cannabinoid receptor 1: 5' exons, candidate regulatory regions, polymorphisms, haplotypes and association with polysubstance abuse. *Molecular Psychiatry*, 9(10):916–31.

Zhang, X.Y. & Kosten, T.A. (2005). Prazosin, an alpha-1 adrenergic antagonist, reduces cocaine-induced reinstatement of drug-seeking. *Biological Psychiatry*, 57(10):1202–1204.

7 Brain imaging and neural circuitry in methamphetamine users

Ernesta M. Meintjes, Anne Uhlmann and Paul Carey

Introduction

Although the effects of illicit drugs on brain structure and function have not been fully characterised, current findings suggest negative neurobiological consequences of adolescent, young adult and adult substance abuse. These include changes in white matter integrity and arrangement, irregularities in cerebral function and disruptions of homeostatic levels of neurotransmitters and brain metabolites, as well as brain structural and functional changes. Brain imaging methodologies have contributed enormously to understanding the psychobiology of addiction (Volkow & Li, 2005; Volkow et al, 2004). Magnetic resonance imaging (MRI), in particular, is a powerful tool with which to probe the varied elements of the neurocircuitry of substance abuse non-invasively.

As has been emphasised in previous chapters, there has recently been a notable increase in South Africa in the abuse of methamphetamine (MA), especially among adolescents and young adults. Worldwide, MA has become one of the fastest-growing illicit drug problems (Rawson & Condon, 2007). It is popular as a party drug because it has both stimulating and hallucinatory effects (Geibprasert et al, 2009). Its principal effects are to increase, through various mechanisms, the synaptic levels of the biogenic amines, dopamine, norepinephrine and serotonin (Goodman et al, 2001; Madras et al, 2005). Accumulating evidence of brain changes following methamphetamine abuse lends support to the notion of toxic effects of methamphetamine on the adult brain.

Structural brain abnormalities associated with MA abuse

Brain morphometry

Bartzokis et al (2000) performed the first controlled study comparing methamphetamine-dependent men with cocaine-dependent men and men who did not use drugs. Total grey matter and white matter volumes were computed by manual tracing of the MR images. In both the substance-abusing groups, temporal lobe total and grey matter volumes were reduced compared to controls, accompanied by larger temporal lobe white matter volumes, while no differences were found in the frontal lobe. The study was limited by the fact that volumes of only parts of the temporal and frontal lobes were quantified. In 2004, Thompson et al found, using a high-resolution surface-based analysis of structural MRI data acquired at 3T, that methamphetamine users displayed less grey matter compared to controls in cingulate, limbic and paralimbic cortices. MA users also demonstrated white matter hypertrophy and smaller hippocampal volumes, the latter being correlated with performance on a word recall test.

Subsequently, a series of studies have examined structural brain abnormalities in MA abusers, often reporting divergent and inconsistent findings. For a summary of these, the reader is referred to an excellent review by Berman and colleagues (Berman et al, 2008). The inconsistency reported in the literature may in part be attributable to the large range of techniques, and their varying properties, that have been employed to analyse structural MRI data. These have included methods such as manual tracing, pattern matching, voxel-based morphometry, tensor-based mapping, cortical thickness mapping, quantification of white matter signal hyperintensities, and diffusion tensor imaging. Studies have also been limited by the use of cross-sectional designs that cannot characterise unambiguously the influence of MA abuse on normal developmental trajectories, while sex differences, severity of MA abuse and the duration of abstinence may account for some of the discrepancies. Despite these limitations, structural brain abnormalities have consistently been reported in MA-abusing subjects compared to healthy non-abusing controls (Berman et al, 2008).

The structural abnormality that has been most consistently reported in MA-abusing subjects is lower cortical grey matter density or volume (Bartzokis et al, 2000; Thompson et al, 2004; Kim et al, 2006; Cowan et al, 2003). Three studies have reported reduced grey matter in the temporal lobe (Bartzokis et al, 2000; Thompson et al, 2004; Cowan et al, 2003), three in the frontal lobe (Thompson et al, 2004; Kim et al, 2006; Cowan et al, 2003), two in the occipital lobe (Thompson et al, 2004; Cowan et al, 2003) and one in the parietal lobe (Thompson et al, 2004). Only one study has reported an increase in cortical grey matter volume, which was localised to the parietal lobe (Jernigan et al, 2005) and was correlated with cognitive impairment.

Of the two studies that have assessed striatal grey matter, both found increased striatal volumes in MA-abusing adults compared to controls (Chang et al, 2005; Jernigan et al, 2005). By contrast, a study of seven-year-old children who had been exposed to MA *in utero* reported smaller striatal volumes compared to healthy non-exposed children (Chang et al, 2004). The authors interpreted these findings as evidence of prenatal dopaminergic neurotoxicity. In adults it has been suggested that increased striatal volume, which has been shown to be associated with better cognitive performance, lower lifetime MA use and greater neuroplasticity, might be a compensatory response to initial neurotoxicity, which might fail above a cumulative neurotoxic load.

Berman et al (2008) noted, however, that similar enlargement of the striatum is induced by neuroleptic treatment of schizophrenic patients. First-generation antipsychotic neuroleptics more frequently cause tardive dyskinesia (TD), and are akin to some of the movement disorders reported in MA abusers (Downes & Whyte, 2005). Since second-generation neuroleptics are, by virtue of differing interaction with dopaminergic receptors, less likely to cause TD, and in some cases may even reverse both TD and enlargement of the striatum (Margolese et al, 2005), Berman et al (2008) suggest that larger basal ganglia volume in MA abusers might provide evidence that direct catecholamine effectors have a high potential for toxicity. Pharmacologic disturbances of catecholamine metabolism, especially dopamine metabolism, may be a generalised way of disturbing iron metabolism and thus producing toxicity in the basal ganglia (Wirshing et al, 1998). It has been demonstrated recently that males have higher iron levels than females (Bartzokis et al, 2007), which suggests that this

mechanism may increase the vulnerability of males to stimulant neurotoxicity, which is consistent with two studies that have reported greater white matter abnormalities in male MA users compared with female MA users (Bae et al, 2006; Chung et al, 2007).

The question now arises how the above mechanism can be reconciled with the notion of striatal enlargement as a compensatory mechanism. Berman et al (2008) propose that dopamine hypersensitivity may be an adaptive response to reduction of dopamine activity in the striatum mediated either through chronic dopaminergic blockade or through amphetamine-mediated loss of dopaminergic terminals. Striatal deficits in children prenatally exposed to MA, which were correlated with cognitive deficits (Chang et al, 2004), suggest that the mechanism that increases local volume to compensate for striatal damage is not available *in utero* (Berman et al, 2008).

White matter abnormalities have been reported more often in MA abusers than grey matter abnormalities. The specific form of white matter abnormality associated with MA use is less clear, since increased volume (Thompson et al, 2004; Chang et al, 2005), decreased volume (Oh et al, 2005; Schlaepfer et al, 2006) and increased white matter hyperintensities (Bae et al, 2006) have all been reported. Since grey matter reductions and white matter expansion are seen in healthy individuals through middle age (Bartzokis et al, 2001), the timing of MRI studies in relation to abuse onset and age of subjects may account for some of the discrepancies.

Diffusion tensor imaging

While studies of white matter volume and white matter hyperintensities (WMH) evaluate macro-structural changes in white matter, diffusion tensor imaging (DTI) allows for the measurement of white matter microstructural integrity (Basser et al, 1994). The most frequently reported measure of white matter integrity is regional fractional anisotropy (FA). FA represents a measure of the degree to which diffusion in the brain region of interest is directional and, in white matter, is therefore sensitive to disorganisation and damage to axons and their myelin sheaths. These will result in reduced directionality and hence lower FA values (for review, see Le Bihan et al, 2001). Although this technique is currently the best tool available to non-invasively give an indication of the overall white matter microstructure, there is a paucity of DTI studies investigating the neuropathology of MA abuse.

Chung and colleagues (2007) were the first to show decreased FA values in the frontal white matter of abstinent MA abusers, which occurred bilaterally in the plane through the anterior and posterior commissure (AC-PC) and in right prefrontal white matter (5 mm above the AC-PC plane), suggesting potential frontal white matter deficits. They also reported a negative correlation between fractional anisotropy in the region of the anterior commissure and the number of errors on the Wisconsin card sorting test (WCST), a measure of executive function. This observation may be an indication of methamphetamine-induced impairment in frontal executive functions like decision-making, which may result from inefficient integration of neural circuits involved in executive function due to compromised white matter integrity. Interestingly, FA and WCST abnormalities were significant only in the male methamphetamine-dependent participants relative to controls, and not in the female subjects. Similar gender differences have been reported in the study by Bae et al (2006), where the more distinct white matter hyperintensities in frontal brain regions of

male MA abusers was described. Chung et al speculate that the female hormone oestrogen may have a neuroprotective effect against the toxicity of methamphetamine. However, a more recent study by Tobias et al (2010) produced contrary results and thus called the matter into dispute, suggesting that an insufficient number of participants of one gender could potentially bias the findings.

A study by Kim and colleagues (2009) demonstrated the impact of methamphetamine abuse on frontal fractional anisotropy in the genu (anterior end) of the corpus callosum in recently abstinent adult populations compared to healthy controls. Here, lower FA correlated inversely with the total error score on the WCST. An additional eigenvalue analysis of the axial and radial water diffusion along myelinated fibres suggested either abnormal myelination or damage to the axonal membrane as being the possible causes of the FA reduction in the genu of the corpus callosum. Similar lower FA values (only trend significant) within the genu of the corpus callosum in methamphetamine abusers were reported in a DTI study by Salo and colleagues (2009). Employing a Stroop selective attention task, this research group also found that lower FA in the genu correlated with an impairment in cognitive control. Both studies' observations support the general notion that damage to frontal brain regions after MA abuse, including frontal white matter as well as linked white matter structures like the corpus callosum, may underlie a variety of cognitive deficits in MA abusers.

In line with earlier findings, a study by Alicata and colleagues (2009) demonstrated lower FA values in frontal white matter, possibly reflecting axonal damage as a result of neuro-inflammation after MA abuse. In spite of reported group differences in the corpus callosum, FA values in the genu in participants with a history of methamphetamine dependence did not differ from controls. However, examining eigenvalue diffusion coefficients, Alicata et al observed higher diffusion in the basal ganglia. This reflects a higher three-dimensional mobility of water in the brain tissue (Le Bihan et al, 2001). Higher diffusion was found in both the putamen and caudate. In addition, diffusion values in the putamen correlated with an earlier age of initial MA use, a higher average daily consumption and a higher lifetime dose of MA. These findings suggest that the basal ganglia are vulnerable to MA exposure and may suffer accompanying inflammation and neurodegeneration.

Most recently, a study by Tobias et al (2010) measured DTI-derived fractional anisotropy in both large slabs and single DTI voxels in several white matter regions and found lower FA in MA abusers compared to healthy controls in regions similar to those reported in earlier studies, namely a region 6 mm above the AC-PC plane in the right prefrontal cortex and in the genu of the corpus callosum. They also observed lower FA values in the right perforant fibres, possibly contributing to neuropathology in the hippocampal formation in MA abusers, as well as bilateral midcaudal superior corona radiata. In addition, FA in the left midcaudal superior corona radiata was shown to correlate with psychiatric symptoms measured with clinical scales.

In summary, various studies have employed *in vivo* comparisons of the brains of participants with a history of methamphetamine dependence to those of healthy controls and demonstrated impaired microstructural white matter integrity using DTI in the frontal cortex, the corpus callosum, basal ganglia and perforant fibres. The data also suggest that

regional changes in white matter integrity, as seen with lower measures of FA, may be correlated with cognitive deficits in MA abusers.

Changes in brain function associated with MA abuse

The translation of the well-characterised pharmacological action of methamphetamine into human brain activation studies is still at a relatively early stage. For instance, the primary sites of action of methamphetamines on the dopamine and other monoamine neurotransmitter systems (Sulzer et al, 2005) do not directly correlate with regional brain functional effects as observed with functional MRI (fMRI). In fact, it is now clear that drugs of abuse seem likely to interact with complex functional and integrated brain circuits, with widespread consequences to brain function. There is, however, clear evidence for an array of effects on frontal, prefrontal and parietal brain function in adult methamphetamine- and stimulant-abusing populations.

Frontal and prefrontal brain regions are considered important in behaviour, cognition and executive functions pertinent to the study of drug abuse. Chronic methamphetamine use is thought to affect frontal and prefrontal brain areas, such as the dorsolateral prefrontal cortex (DLPFC) which coordinates higher-order cognitive functions, including aspects of memory, decision-making, affective processing, behavioural inhibition and problem-solving. The mid-DLPFC mediates working memory, including higher attentional functions, while the inferior prefrontal cortex (PFC) is thought to be involved in inhibition (Milham et al, 2003).

Studies of the effects of methamphetamine abuse have shown that brain activation in response to tests of prediction failed to involve ventromedial and DLPFC regions, taking into account the influencing effects of preceding trial outcomes (Paulus et al, 2002). Further work on decision-making has found that methamphetamine-dependent subjects show lower success-independent activation of the DLPFC, anterior cingulate, parietal and orbitofrontal cortex (OFC) than control subjects (Paulus et al, 2003). Unlike healthy control participants, who showed a success-related activation of the DLPFC, OFC and parietal cortex, in MA abusers the magnitude of activation correlated with the unpredictability of decision-making outcomes.

Similar experimental work by the same group also found that the magnitude of brain activation of the right insular, posterior cingulate and temporal cortex accurately predicted relapse in the majority of MA-abstinent subjects (Paulus et al, 2005). Methamphetamine-induced changes in brain activation, especially in the frontal brain regions, seem to compromise decision-making processes. This might explain the limited cognitive control and the consequent impairment of good judgment in MA abusers.

Accordant behavioural observations were made in decision-making studies involving the choice between a smaller immediate reward and a larger but delayed reward (delay discounting task). Methamphetamine abusers tend to have a prominent preference for the smaller, immediate reward and tend to devalue rewards for which they must wait (Hoffman et al, 2008; Monterosso et al, 2007), seemingly exhibiting a diminished capacity for self-control. In addition, MA abusers show different task-related brain activation patterns

when compared to healthy control subjects. More specifically, there is less activation in the dorsolateral prefrontal cortex, precuneus and anterior cingulate cortex during delay discounting tasks (Hoffman et al, 2008).

In contrast to decision-making studies, which repeatedly showed lower DLPFC activity in MA abusers, a study examining empathy processing showed a greater task-related DLPFC activity in MA abusers than in healthy control subjects (Kim et al, 2010). The authors suggest that an empathy task may make different demands of the DLPFC than a two-choice prediction task, and therefore requires a different function of that brain region. Kim et al further propose that the DLPFC, which is not generally activated in empathy processing, may exhibit greater activation in MA abusers to compensate for the dysfunction of the OFC, temporal lobes and hippocampus: a neural network linked to episodic memory and the processing of socio-emotional information. However, the DLPFC overactivation does not appear to be sufficient to compensate for the dysfunction in the empathy network, which might explain the difficulty that MA abusers have with interpersonal communication and relationships (Kim et al, 2010).

The anterior cingulate cortex (ACC) subsumes a complex array of functions that are broadly concerned with aspects of cognitive control and decision-making (Vogt et al, 1992) in the presence of distracting or competing internal or external cues. As such, the ACC has an important function in integrating sensory and affective processes to moderate behavioural and emotional responses. In stimulant abuse, studies of cognitive control show less pronounced brain activation in response to a go/no-go task in recently abstinent MA abusers (Leland et al, 2008). This study demonstrated that certain cues in the task predicting the need to inhibit responses in the following trial led to an ACC activation in MA abusers, which in turn was positively correlated with the subject's inhibitory performance. By contrast, there was no cue-related ACC activation in healthy control subjects. Therefore, the authors suggest that the ACC may predict to what extent advanced warning may diminish inhibitory difficulties in methamphetamine-dependent individuals.

In a variant of the Stroop paradigm, however, interference produced lower activation of the right prefrontal cortex in cognitively primed methamphetamine abusers, resulting in their making more errors and having slower reaction times in comparison to healthy control subjects, but there was no difference in conflict-related activation of the ACC (Salo et al, 2009). This data suggests a limited ability in methamphetamine abusers to modify behaviour following an experience, a maladjustment which is associated with abnormal PFC activation and may be a factor indicating the persistence of substance use disorders. However, experiments indicate that drug-related behaviours such as craving result in excess activation of the ACC in drug-addicted subjects (Goldstein & Volkow, 2002). The authors note that the state of the ACC may play an important role in the craving experience and the maintenance of drug addiction through the loss of self-control. As such, the differences in activation of the ACC, between MA abusers and healthy subjects, can only be considered in the context of the activation paradigm being employed. Overall, these findings suggest that the ACC is involved in the cognitive and behavioural changes associated with methamphetamine abuse.

The parietal cortex plays an important role in attention, visuo-spatial function and in aspects of working memory (Cabeza & Nyberg, 2000). It is richly and bi-directionally

connected to the insula, striatum, ACC and DLPFC. Consequently, its functions in respect to emotional processing and decision-making are relevant to the study of substance use disorders. Specific cognitive functions, including voluntary control of attention (Hopfinger et al, 2000) and cognitive inhibitory control (Garavan et al, 1999), have similar relevance. A study of decision-making and success rates, as mentioned above, was found to influence a wide range of interconnected brain regions, including the inferior parietal lobule and precuneus (Paulus et al, 2003). The attenuated, task-related activation of areas in the parietal cortex, as shown in this study, may lead to the modified processing of errors and success in MA abusers, which leaves them more stimulus-driven during decision-making.

Because of its capacity to compare functional differences in individual neural networks, functional magnetic resonance imaging (fMRI) provides a unique tool to study dysfunctions in discrete brain circuits and, consequently, disrupted cognitive and affective processes. In summary, the reviewed studies show that methamphetamine dependence is characterised by a widespread alteration of the activation of structures in the frontal cortex, ACC and parietal cortex – brain regions involved with specific cognitive and emotional processes. A reduced capacity to activate specific brain areas contributes to the inadequate processing of information, resulting in impaired inhibitory control, executive function, memory and decision-making, as well as impaired socio-emotional behaviours in MA abusers.

Metabolic changes associated with MA abuse

In examining changes in neuronal metabolites in specific brain regions in methamphetamine use disorders, magnetic resonance spectroscopy (MRS) has been almost exclusively confined to ^{1}H (proton) techniques. A non-invasive imaging tool, MRS utilises pulse sequences to measure relative concentrations of specific metabolites, including N-acetylaspartate (NAA, measure of neuronal viability), choline (Cho, cell membrane synthesis or degradation product), myo-inositol (mI, glial marker) and creatine (Cr, high-energy metabolic product) (Nordahl et al, 2005). As these metabolites are markers of cellular integrity and function, MRS can identify and assess the presence of neuronal damage in human subjects.

In the first MRS study of methamphetamine-abusing subjects, Ernst, Chang, Leonido-Yee and Speck (2000) found abnormally low NAA in the basal ganglia and a trend for reduction in frontal white and grey matter in recently abstinent MA abusers compared to healthy control subjects. The decrease in frontal white matter NAA was found to be dependent on the individual's cumulative lifetime MA dose. These findings may provide evidence for neuronal loss and long-term neuronal damage in abstinent MA abusers. In the frontal grey matter, abnormally high levels of Cho and mI were interpreted as a sign of glial proliferation, most likely in response to neuronal toxicity produced by methamphetamine.

Similar findings of lower NAA concentrations in frontal white matter and their inverse correlation with the cumulative MA dose, as well as higher levels of mI were reported in a more recent study conducted by Sung and colleagues (Sung et al, 2007). Lower NAA concentrations were found in MA abusers with a 'large' cumulative dose (>100g) relative to those with a 'small' cumulative dose. NAA concentration in frontal grey matter did not differ significantly between the two abusing groups. Concentrations did, however, correlate with the duration of abstinence. Sung et al concluded that with prolonged abstinence,

MA-related abnormalities in grey matter regions may partly recover, whereas in white matter, recovery seems limited.

In one of the few studies on methamphetamine-related psychosis, Sekine, Minabe, Kawai et al, (2002) found an elevated Cho/Cr ratio in the bilateral basal ganglia of abstinent MA abusers (4 months to 4 years). This increased ratio correlated with duration of MA abuse and the severity of residual psychiatric symptoms. In contrast, NAA/Cho ratios in the basal ganglia did not differ between MA abusers and healthy control subjects. These findings suggest that the onset and persistence of psychiatric symptoms in abstinent users relates in part to enduring metabolite changes in the basal ganglia.

Consistent with neural damage to the frontostriatal regions, a study by Nordahl and colleagues (2002) found lower NAA/Cr ratios in the anterior cingulate cortex (ACC) in MA abusers during early abstinence (mean 9.3 weeks), whereas Cho/Cr ratios were higher in this brain region. In a follow-up study the same group (Nordahl et al, 2005) were able to demonstrate that low NAA/Cr ratios in MA abusers persist in the ACC even after long periods of abstinence (mean 3 years), whereas levels of Cho/Cr in the ACC approach those of normal controls. Furthermore, NAA/Cr was negatively correlated with duration of MA use, while Cho/Cr correlated negatively with duration of abstinence. The authors suggested that relative changes in brain metabolite concentrations due to MA abuse might involve different processes. The evidence of metabolic alterations in the ACC in MA abusers may, along with the observed functional deficits in this brain area, explain some of the behavioural and cognitive impairments associated with MA abuse (Nordahl et al, 2002).

In a subsequent MRS study by Salo and colleagues (Salo et al, 2007), the relationship between changes in brain metabolite levels and cognitive impairments in MA abusers was shown by employing a selective Stroop attention task. Lower levels of NAA/Cr within the anterior cingulate cortex correlated with the reduced attentional control exhibited by the MA abusers. Concentrations of Cho/NAA were elevated in the ACC, but did not show a correlation with cognitive performance. However, these findings suggest that long-term MA abuse compromises the neuronal integrity of the ACC, leading to the impaired regulation of cognitive mechanisms.

One of the most recent studies using MRS to study the effects of MA abuse assessed the concentration of the neurotransmitter glutamate plus glutamine (GLX) during abstinence from MA abuse (Ernst & Chang, 2008). MA abusers showed lower GLX levels in frontal grey matter after a short period of abstinence (<1 month) than healthy control subjects. After prolonged abstinence (5 months), however, frontal grey matter GLX concentrations tended to correlate with the duration of abstinence. The authors suggested that reduced GLX levels in recently abstinent MA abusers might gradually reverse after longer periods of abstinence. Whether the MA-related changes in the GLX system reverse completely remains unclear.

These MRS studies collectively demonstrate the neurotoxic effects of chronic methamphetamine exposure, manifested as neural injury and associated inflammatory response in the frontal and striatal brain regions, demonstrated by changes in the different metabolite concentrations. The neural marker NAA or NAA-to-total-creatine ratio (NAA/tCr) may be decreased in frontal regions and the striatum and, furthermore, appears to be related to the total lifetime exposure to MA and cognitive impairment in MA abusers. The glial

markers Cho, Cho/Cr and mI have been shown to be present in increased concentrations in the frontal lobes, which may account for residual psychiatric symptoms in MA abusers. MA-related changes in metabolite concentrations occur in white as well as grey matter and have been found to be dose-dependent. Findings from MRS studies suggest that the neurotoxicity of MA is both region- and metabolite-specific.

Conclusion

Modern brain imaging techniques have advanced the specificity with which investigators are now able to delineate the impact of MA use in a variety of clinical and preclinical settings. These findings suggest overall that widespread effects on brain function, structure and chemistry correlate with impairments in social, cognitive and behavioural function. These studies emphasise that the brain of MA abusers is likely to be vulnerable to damaging effects that endure to varying degrees. The timing of the insult, lifetime dose and comorbidity with other substances of abuse and psychiatric symptoms predict the severity and persistence of most patterns of change observed.

Studies of the effects of MA on brain structure and function suffer from several important limitations. Most studies use a cross-sectional design. As such, inferences from observed group differences regarding high-risk or protective factors for developing addiction, whether these changes directly represent brain damage or are compensatory responses to such damage, and what predictive value findings have for long-term deficits and functional impairment, remains unclear.

We have not reviewed the important contribution of molecular imaging (eg, SPECT and PET) (Chang et al, 2007) to understanding the neurobiology of MA use and abuse. MRI and molecular imaging techniques should be combined with genetic, neuropsychological and phenomenological data in prospective designs in adult, adolescent and at-risk populations in order to delineate more fully the psychobiological mechanisms underlying MA-related disorders. Ultimately, such work may contribute to preventive and therapeutic interventions.

References

Alicata, D., Chang, L., Cloak, C., Abe, K. & Ernst, T. (2009). Higher diffusion in striatum and lower fractional anisotropy in white matter of methamphetamine users. *Psychiatry Research*, 174(1):1–8.

Bae, S.C., Lyoo, I.K., Sung, Y.H., et al. (2006). Increased white matter hyperintensities in male methamphetamine abusers. *Drug and Alcohol Dependence*, 81(1):83–88.

Bartzokis, G., Beckson, M., Lu, P.H., Edwards, N., Rapoport, R., Wiseman, E. & Bridge, P. (2000). Age-related brain volume reductions in amphetamine and cocaine addicts and normal controls: implications for addiction research. *Psychiatry Research. Neuroimaging*, 98(2):93–102.

Bartzokis, G., Beckson, M., Lu, P.H., Nuechterlein, K.H., Edwards, N. & Mintz, J. (2001). Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. *Archives of General Psychiatry*, 58(5):461–65.

Bartzokis, G., Tishler, T.A., Lu, P.H., Villablanca, P., Altshuler, L.L., Carter, M., Huang, D., Edwards, N. & Mintz, J. (2007). Brain ferritin iron may influence age- and gender-related risks of neurodegenration. *Neurobiology of Aging*, 28(3):414–23.

Basser, P.J., Mattiello, J. & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, 66(1):259–67.

Berman, S., O'Neill, J., Fears, S., Bartzokis, G. & London, E.D. (2008). Abuse of amphetamines and structural abnormalities in the brain. *Annals of the New York Academy of Sciences*, 1141:195–220.

Cabeza, R. & Nyberg, L. (2000). Imaging cognition II. An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*, 12(1):1–47.

Chang, L., Alicata, D., Ernst, T. & Volkow, N. (2007). Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. *Addiction*, 102(Suppl. 1):16–32.

Chang, L., Cloak, C., Patterson, K., Grob, C., Miller, E.N. & Ernst. T. (2005). Enlarged striatum in abstinent methamphetamine abusers: a possible compensatory response. *Biological Psychiatry*, 57(9):967–74.

Chang, L., Smith, L.M., LoPresti, C., Yonekura, M.L., Kuo, J., Walot, I. & Ernst, T. (2004). Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatry Research*, 132(2):95–106.

Chung, A., Lyoo, I.K., Kim, S.J. Hwang, J., Bae, S.C., Sung, Y.H., Sim, M.E., Song, I.C., Kim, J., Chang, K.H. & Renshaw, P.F. (2007). Decreased frontal white-matter integrity in abstinent methamphetamine abusers. *The International Journal of Neuropsychopharmacology*, 10(6):765–75.

Cowan, R.L., Lyoo, I.K., Sung, S.M., Ahn, K.H., Kim, M.J., Hwang, J., Haga, E., Vimal, R.L., Lukas, S.E. & Renshaw, P.F. (2003). Reduced cortical gray matter density in human MDMA (ecstasy) users: a voxel-based morphometry study. *Drug and Alcohol Dependence*, 72(3):225–35.

Downes, M.A. & Whyte, I.M. (2005). Amphetamine-induced movement disorder. *Emergency Medicine Australasia*, 17(3):277–80.

Ernst, T. & Chang, L. (2008) Adaption of brain glutamate plus glutamine during abstinence from chronic methamphetamine abuse. *Journal of Neuroimmune Pharmacology*, 3(3):165–72.

Ernst, T., Chang, L., Leonido-Yee, M. & Speck, O. (2000). Evidence for long-term neurotoxicity associated with methamphetamine abuse a HMRS study. *Neurology*, 54(6):1344–49.

Garavan, H., Ross, T.J. & Stein, E.A. (1999). Right hemispheric dominance of inhibitory control: an event-related functional MRI study. *Proceedings of the National Academy of Sciences*, 96(14):8301–306.

Geibprasert, S., Gallucci, M. & Krings, T. (2010). Addictive illegal drugs: structural neuroimaging. *American Journal of Neuroradiology*, 31(5):803–808.

Goldstein, R.Z. & Volkow, N.D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex [review]. *American Journal of Psychiatry*, 159(10):1642–52.

Goodman, L.S., Hardman, J.G., Limbird, L.E. & Gilman, A.G. (2001). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York: McGraw-Hill.

Hoffman, W.F., Schwartz, D.L., Huckans, M.S., McFarland, B.H., Meiri, G., Stevens, A.A., & Mitchell, S.H. (2008). Cortical activation during delay discounting in abstinent methamphetamine dependent individuals. *Psychopharmacology*, 201(2):183–93.

Hopfinger, J.B., Buonocore, M.H. & Mangun, G.R. (2000). The neural mechanisms of top-down attentional control. *Nature Neuroscience*, 3:284–91.

Jernigan, T.L., Gamst, A.C., Archibald, S.L., Fennema-Notestine, C., Mindt, M.R., Marcotte, T.D., Heaton, R.K., Ellis, R.J. & Grant, I. (2005). Effects of methamphetamine dependence and HIV infection on cerebral morphology. *American Journal of Psychiatry*, 162(8):1461–72.

Kim, I.S., Kim, Y.T., Song, H.J., Lee, J.J., Kwon, D.H., Lee, H.J., Kim, M.N., Yoo, D.S. & Chang, Y. (2009). Reduced corpus callosum white matter microstructural integrity revealed by diffusion tensor eigenvalues in abstinent methamphetamine addicts. *Neurotoxicology*, 30(2):209–13.

Kim, S.J., Lyoo, I.K., Hwang, J., Chung, A., Hoon Sung, Y., Kim, J., Kwon, D.H., Chang, K.H. & Renshaw, P.F. (2006). Prefrontal grey-matter changes in short-term and long-term abstinent methamphetamine abusers. *The International Journal of Neuropsychopharmacology*, 9(2):221–28.

Kim, Y.T., Lee, J.J., Song, H.J., Kim, J.H., Kwon, D.H., Kim, M.N., Yoo, D.S., Lee, H.J., Kim, H.J. & Chang, Y. (2010). Alterations in cortical activity of male methamphetamine abusers performing an empathy task: fMRI study. *Human Psychopharmacology*, 25(1): 63–70.

Le Bihan, D., Mangin, J.-F., Poupon, C., Clark, C.A., Pappata, S., Molko, N. & Chabriat, H. (2001). Diffusion tensor imaging: concepts and applications. *Journal of Magnetic Resonance Imaging*, 13(4):534–46.

Leland, D.S., Arce, E., Miller, D.A. & Paulus, M.P. (2008). Anterior cingulate cortex and benefit of predictive cueing on response inhibition in stimulant dependent individuals. *Biological Psychiatry*, 63(2):184–90.

Madras, B.K., Miller, G.M. & Fischman, A.J. (2005). The dopamine transporter and attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 57(11):1397–409.

Margolese, H.C., Chouinard, G., Kolivakis, T.T., Beauclair, L. & Miller, R. (2005). Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 1: pathophysiology and mechanisms of induction. *Canadian Journal of Psychiatry*, 50(9):541–47.

Milham, M.P., Banich, M.T. & Barad, V. (2003). Competition for priority in processing increases prefrontal cortex's involvement in top–down control: an event-related fMRI study of the Stroop task. *Brain Research. Cognitive Brain Research*, 17(2):212–22.

Monterosso, J.R., Ainslie, G., Xu, J., Cordova, X., Domier, C.P. & London, E.D. (2007). Frontoparietal cortical activity of methamphetamine dependent and comparison subjects performing a delay discounting task. *Human Brain Mapping*, 28(5):383–93.

Nordahl, T.E., Salo, R., Natsuaki, Y., Galloway, G.P., Waters, C., Moore, C.D., Kile, S. & Buonocore, M.H. (2005). Methamphetamine users in sustained abstinence: a proton magnetic resonance spectroscopy study. *Archives of General Psychiatry*, 62(4):444–52.

Nordahl, T.E., Salo, R., Possin, K., Gibson, D.R., Flynn, N., Leamon, M., Galloway, G.P., Pfefferbaum, A., Spielman, D.M., Adalsteinsson, E. & Sullivan, E.V. (2002). Low N-acetyl-aspartate and high choline in the anterior cingulum of recently abstinent

methamphetamine-dependent subjects: a preliminary proton MRS study. *Psychiatry Research*, 116(1–2):43–52.

Oh, J.S., Lyoo, I.K., Sung, Y.H., Hwang, J., Kim, J., Chung, A., Park, K.S., Kim, S.J., Renshaw, P.F. & Song I.C. (2005). Shape changes of the corpus callosum in abstinent methamphetamine users. *Neuroscience Letters*, 384(1–2):76–81.

Paulus, M.P., Hozack, N., Frank, L., Brown, G.G. & Schuckit, M.A. (2003). Decision making by methamphetamine-dependent subjects is associated with error-rate-independent decrease in prefrontal and parietal activation. *Biological Psychiatry*, 53(1):65–74.

Paulus, M.P., Hozack, N.E., Zauscher, B.E., Frank, L., Brown, G.G., Braff, D.L., & Schuckit, M.A. (2002). Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. *Neuropsychopharmacology*, 26(1):53–63.

Paulus, M.P., Tapert, S.F. & Schuckit, M.A. (2005). Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Archives of General Psychiatry*, 62(7):761–68.

Payer, D.E., Lieberman, M.D., Monterosso, J.R., Xu, J., Fong, T.W. & London, E.D. (2008). Differences in cortical activity between methamphetamine-dependent and healthy individuals performing a facial affect matching task. *Drug and Alcohol Dependence*, 93(1–2):93–102.

Rawson, R.A. & Condon, T.P. (2007) Why do we need an addiction supplement focused on methamphetamine? *Addiction*, 102(Suppl. 1):1–4.

Salo, R., Nordahl, T.E., Buonocore, M.H., Natsuaki, Y., Waters, C., Moore, C.D., Galloway, G. P. & Leamon, M.H. (2009). Cognitive control and white matter callosal microstructure in methamphetamine-dependent subjects: a diffusion tensor imaging study. *Biological Psychiatry*, 65(2):122–28.

Salo, R., Nordahl, T.E., Natsuaki, Y., Leamon, M.H., Galloway, G.P., Waters, C., Moore, C.D. & Buonocore, M.H. (2007). Attentional control and brain metabolite levels in methamphetamine abusers. *Biological Psychiatry*, 61(11):1272–80.

Salo, R., Ursu, S., Buonocore, M.H., Leamon, M.H. & Carter, C. (2009). Impaired prefrontal cortical function and disrupted adaptive cognitive control in methamphetamine abusers: a functional magnetic resonance imaging study. *Biological Psychiatry*, 65(8):706–709.

Schlaepfer, T.E., Lancaster, E., Heidbreder, R., Strain, E.C., Kosel, M., Fisch, H.U. & Pearlson, G.D. (2006). Decreased frontal white-matter volume in chronic substance abuse. *The International Journal of Neuropsychopharmacology*, 9(2):147–53.

Sekine, Y., Minabe, Y., Kawai, M., Suzuki, K., Iyo, M., Isoda, H., Sakahara, H., Ashby, C.R., Jr, Takei, N. & Mori, N. (2002). Metabolite alterations in basal ganglia associated with methamphetamine-related psychiatric symptoms. A proton MRS study. *Neuropsychopharmacology*, 27(3):453–61.

Sulzer, D., Sonders, M.S., Poulsen, N.W. & Galli, A. (2005). Mechanisms of neurotransmitter release by amphetamines: a review. *Progress in Neurobiology*, 75(6):406–33.

Sung, Y., Cho, S., Hwang, J., Kim, S.J., Kim, H., Bae, S., Kim, N., Chang, K.H., Daniels, M., Renshaw, P.F. & Lyoo I.K. (2007). Relationship between N-acetyl-aspartate in gray and white matter of abstinent methamphetamine abusers and their history of drug abuse: A proton magnetic resonance spectroscopy study. *Drug and Alcohol Dependence*, 88(1):28–35.

Thompson, P.M., Hayashi, K., Simon, S.L., Geaga, J.A., Hong, M.S., Sui, Y., Lee, J.Y., Toga, A.W., Ling, W. & London, E.D. (2004). Structural abnormalities in the brains of human subjects who use methamphetamine. *Journal of Neuroscience*, 24(26):6028–36.

Tobias, M.C., O'Neill, J., Hudkins, M., Bartzokis, G., Dean, A.C. & London, E.D. (2010). White-matter abnormalities in brain during early abstinence from methamphetamine abuse. *Psychopharmacology*, 209(1):13–24.

Vogt, B.A., Finch, D.M. & Olson, C.R. (1992). Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cerebral Cortex*, 2(6):435–43.

Volkow, N.D., Fowler, J.S., Wang, G.J. & Swanson, J.M. (2004). Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Molecular Psychiatry*, 9:557–69.

Volkow, N. & Li, T.K. (2005). The neuroscience of addiction. *Nature Neuroscience*, 8:1429–30.

Wirshing, D.A., Bartzokis, G., Pierre, J.M., Wirshing, W.C., Sun, A., Tishler, T.A. & Marder, S.R. (1998). Tardive dyskinesia and serum iron indices. *Biological Psychiatry*, 44(6):493–98.

8 Affective neuroscience of methamphetamine abuse

Susan Malcolm-Smith, Anne Uhlmann, Anthony Hodge and Jonathan Ipser

Introduction

As indicated in previous chapters, abuse of the synthetic psychostimulant methamphetamine has recently become a serious problem in the Western Cape, especially in poorer communities. Cape Town, in particular, has seen an increasing trend over the last decade, with up to 35% of patients seeking treatment for addiction reporting methamphetamine as their primary drug of abuse. The majority of these patients are male adolescents or young adults, with 30% reportedly under 20 years of age in 2008 (Plüddemann, Myers & Parry, 2009).

Of particular relevance for this chapter are the significant social and interpersonal problems associated with methamphetamine abuse. Although these tend to be reported less frequently than the immediate effects to individual health (Sommers, Baskin & Baskin-Sommers, 2006), methamphetamine abuse leads to substantial disruptions within the family, along with marked difficulties in school or work environments. In addition to the direct public-health consequences of methamphetamine intoxication, use of this drug also results in secondary social costs, which include an increased propensity for violence and drug-related crime (Obot, Poznyak & Monteiro, 2004).

It is by now well established that methamphetamines are highly neurotoxic, and impair the regulation of aggressive behaviour to a greater extent than other substances of abuse (Baicy & London, 2007). Drug-related neuroscience investigates the effect of chemical intake on the brain's structure and functioning, thereby giving insight into the associated effects on affect, behaviour and cognition. Recent years have seen an increased interest in the neural basis of the emotional and social deficits associated with drug use, and this chapter will highlight the importance of an affective neuroscience approach in understanding these impairments in methamphetamine abusers.

Although some of the information on neurochemistry and neuroanatomy may overlap with that presented in other chapters, we focus specifically on aspects of affective and social function that are affected by prolonged methamphetamine abuse. These include reward sensitivity, mood, impulsivity and aggression, and emotionally mediated social behaviour. A substantial literature based on animal work exists, in contrast to comparatively sparse work done on humans. Although the insights gained from animal research are invaluable, we have chosen, in light of inter-species variability, to focus on what is known specifically about the effects of methamphetamine in humans, referring to animal work only where necessary.

Reward sensitivity

The precise mechanisms of addiction and withdrawal have yet to be fully elucidated, but alteration in the function of brain reward circuitry is clearly implicated. Psychostimulants powerfully stimulate reward circuitry (Koob, 2009), but over time they create changes in reward sensitivity that result in dysfunction in the ability to experience positive hedonic states related to a variety of natural rewards, and contribute to withdrawal effects. Over time, adaptation to the euphoric effects of methamphetamine occurs, mediated primarily by dopaminergic pathways in the brain. Abusers thus require increasing doses of the drug to achieve the same reward experience. Furthermore, the withdrawal state following intoxication becomes increasingly aversive in the long term, characterised by negative affect such as depression, anxiety, heightened irritability and paranoia. Drug use then becomes a method to escape these aversive symptoms (Meredith et al, 2005).

Methamphetamine elevates the levels of extracellular monoamine neurotransmitters, including the catecholamines dopamine and norepinephrine, as well as serotonin. Of particular relevance is the increase in levels of dopamine in the striatum, especially the ventral striatum (nucleus accumbens), and in the prefrontal cortex (see Figures 2 and 6.2) (Sulzer et al, 2005). These circuits are integrally involved in reward processes. Dopamine levels are increased via various mechanisms that are not yet fully articulated. We do know that methamphetamine stimulates dopamine release, in part via reverse transport, and also acts to block its uptake. Furthermore, it reduces dopamine transporter availability and also appears to reduce transporter efficacy. This action on the transporters contributes to increases in synaptic levels of dopamine (Saunders et al, 2000). Moreover, methamphetamine has been shown to promote dopamine synthesis, and it acts as a monoamine oxidase inhibitor (Sulzer et al, 2005). The rewarding properties of methamphetamine are thus strongly tied to this ability to raise dopamine levels.

Methamphetamine intake produces intensely pleasurable and rewarding states, which increases the likelihood of repeated use of the drug. Imaging work in humans is corroborating extensive animal work that indicates that psychostimulant drugs promote elevated levels of dopamine, which, as indicated above, is implicated in reward processes. A study by Völlm and colleagues (2004) demonstrated that, in contrast to saline administration, intravenous infusions of methamphetamine (0.15 mg/kg) administered to seven healthy psychostimulant-naïve subjects produced activity in reward-related areas of the human brain, including the medial orbitofrontal cortex, the rostral anterior cingulate cortex and the ventral striatum. These activations correlated with subjective behavioural ratings of 'mind-racing' produced by methamphetamine administration. A series of PET studies conducted by Volkow and colleagues (reviewed in Volkow et al, 2002) have helped to illustrate the role of dopamine and reward circuitry in human response to psychostimulants. These authors have shown that increased dopamine levels subsequent to methylphenidate dosing correlate significantly with subjective reports of highly positive affective states in healthy subjects (Volkow et al, 1999). Volkow and colleagues go on to suggest that reduced or low D_2 receptor density may be implicated in vulnerability to addiction.

The observation that elevated dopamine and euphoria occur in both addicts and non-addicts indicates that pleasurable responses to methamphetamine abuse cannot fully account for addiction. In contrast to the rewarding states experienced with methamphetamine use,

withdrawal is characterised by a hypodopaminergic state, featuring reduced dopamine release and reduction in dopamine D_2 receptors. Volkow and her colleagues suggest that this altered neurochemistry results in reduced sensitivity to natural rewards, and to the anhedonia and negative mood states associated with withdrawal. They argue that these features contribute to promoting ongoing drug use, which serves to compensate for the dopaminergic deficits. They have further shown that reduced D_2 receptor density is associated with reduced activity in the orbitofrontal and anterior cingulate cortex (Volkow et al, 2001), and suggest this is one mechanism by which dysregulated dopamine function leads to loss of the ability to regulate behaviour and to compulsive drug use. In animals, damage to these circuits results in perseverative behaviour and resistance to extinction of previously reward-conditioned behaviours. In humans who suffer injury to these regions, poor behavioural control and poor emotion regulation are commonly observed. These authors thus conclude that dopamine dysregulation in the fronto-striatal circuitry, which regulates motivation, drive and self-control, is a key contributor to addiction.

The question of how reward thresholds or reward sensitivity changes with ongoing use of methamphetamine remains an area of active investigation. The phenomenon of sensitisation to the drug appears to be critical. In animals, repeated exposure to methamphetamine leads to sensitised behavioural and neural responses to the drug (Sarkar & Kornetsky, 1995). This process seems to contribute to the drug's acquisition of increasing motivational value. Two seemingly contradictory dopamine effects appear to occur with repeated exposure: firstly, a compensatory adaptation featuring reduced mesolimbic dopamine results in reduced motivation, particularly concerning non-drug-related activities; secondly, dopamine responsiveness to methamphetamine is enhanced, or sensitised, which is thought to contribute to drug-related associations acquiring increased incentive salience (Alcaro, Huber & Panksepp, 2007).

Reward sensitivity has been implicated in forming associations between drug-related cues (unconditioned stimuli) and previously neutral stimuli (conditioned stimuli) (Koob, 2009). Once this association has formed, presentation of the conditioned stimuli elicits symptoms of craving in drug users (Baicy & London, 2007). Cue-elicited craving may occur a considerable time after the withdrawal symptoms have subsided (Alcaro, Huber & Panksepp, 2007), suggesting that methamphetamine addiction causes long-term alterations in the structure and functioning of brain regions associated with reward sensitivity and conditioning. The exact mechanism underlying the transition from methamphetamine-liking to methamphetamine-craving still needs to be elucidated, but it could involve a 'pathological learning' process associated with the abnormal regulation of dopamine levels (Hyman, 2005).

Functional imaging studies support the notion of long-term changes in reward sensitivity following methamphetamine abuse. Positron emission tomography (PET) studies have revealed that dopamine transporter density may be particularly vulnerable, as it is substantially reduced not only while drug abuse is current, but also in the longer term. PET studies conducted by Sekine and colleagues (2001; 2003) have shown reduced expression of dopamine transporters in key regions in methamphetamine users versus healthy controls. Reductions were found in the ventral striatum, orbitofrontal cortex and amygdala. These correlated with length of methamphetamine use and with psychiatric symptoms. Long-term

down-regulation of dopamine transporters in the striatum has been shown in PET studies of primates (Villemagne et al, 1998). These findings were replicated in a study of humans by McCann and colleagues (1998). They reported that dopamine transporter density remained down-regulated in six methamphetamine abusers after approximately three years of abstinence. Given dopamine's crucial role in the regulation of both emotional responses and the reward system, such major changes to this system indicate an ongoing impact on the individual's ability to process reward-related behaviour in an appropriate manner.

An important perspective is provided by Panksepp's psychobiological model of emotion, one of the most prominent theories in the emerging discipline of affective neuroscience (Panksepp, 2005). This model proposes that the hedonic states associated with dopamine release and activation of the cortico-striatal circuitry involved in reward processes are in fact embedded in a core evolved emotion system. Termed the 'SEEKING system', this system is thought to have evolved as the neural basis for motivation, affective drive and non-specific but directed instinctual exploratory activity, such as foraging. The SEEKING system has its neural correlates in the mesolimbic dopamine system, particularly in the periaquaductal grey, ventral tegmental area and hypothalamus, with projections to the basal ganglia and thalamocortical circuits via mid-brain dopaminergic neurons (Alcaro, Huber & Panksepp, 2007). Its activation is characterised by a highly positive state of engagement with the world, and eagerness to engage in a variety of goal-directed activities.

Conceptualising addiction as dysregulation of a core evolved emotion system – similar to those for fear or anger – lends depth to our perspective of affective dysregulation as a core component of the sequelae of methamphetamine abuse, and adds to our ability to grasp the subjective experience of addiction. The possibility that methamphetamine abuse creates changes in this neurocircuitry that may outlast actual drug use has serious implications for long-term outcome prospects, and certainly warrants a great deal more research.

Anxiety and depression

Methamphetamine abusers are at an increased risk of being diagnosed with affective disorders, such as major depressive disorder and anxiety disorders (Meredith et al, 2005; Plüddemann et al, 2009). Zweben and colleagues (2004) examined psychiatric symptoms in a large cohort of methamphetamine users and found very high scores on depression scales, with those scores being positively correlated with frequency of use. Specifically, 68% of all female and 50% of all male users reported feeling depressed at some point in their life.

One of the defining characteristics of a drug addiction is the emergence of a negative affective state during the withdrawal phase (Koob, 2009). Depression and anxiety are the most commonly reported negative emotions occurring during the withdrawal associated with methamphetamine addiction. As discussed in the previous section, with prolonged drug use reward thresholds are raised (Koob, 2009), especially for non-drug-related stimuli (Alcaro, Huber & Panksepp, 2007). These increased reward thresholds very likely contribute towards the marked depressive symptoms reported by abstinent methamphetamine abusers. This negative affect serves to increase the likelihood that the recovering addict 'falls off the wagon', in line with findings that difficulties in regulating emotion constitute a risk factor for subsequent methamphetamine abuse (Obot et al, 2004).

Looking to the literature on the possible contribution of altered neural structure or function to the increased incidence of mood disorders subsequent to methamphetamine abuse, it appears that relatively limited work in humans has been done. Recent structural magnetic resonance imaging (MRI) studies have reported several morphological changes in both grey and white matter tissue in the brains of methamphetamine abusers, compared to healthy control subjects, which may underlie negative affect. Thompson and colleagues (2004) reported marked loss of grey matter particularly in the cingulate and limbic cortices of a sample of 22 methamphetamine abusers, regions that have been implicated in affect regulation and in depression. They also detected significantly reduced hippocampal volume and white-matter-hypertrophy in mesial temporal regions in this group relative to healthy controls. These findings led them to suggest that these structural changes may contribute to symptoms of depression and anxiety in active chronic methamphetamine abusers.

In addition to a possible link to structural impairments, a PET study by London et al (2004) indicated that mood disturbances in 17 abstaining (4–7 days) methamphetamine abusers were associated with changes in brain glucose metabolism. Methamphetamine abusers had higher scores on self-rating scales of depression and anxiety compared with non-users, as well as alterations in glucose metabolism in several limbic regions, including orbitofrontal cortex, ventral striatum, insula and amygdala. Hypoactivity was observed in the anterior cingulate cortex and insula, while hyperactivity was noted in orbitofrontal cortex and ventral striatum. The most robust alterations were found in the subgenual anterior cingulate, which has repeatedly been associated with depression, and in the ventral striatum, which is critically involved in reward states. Associations between altered glucose metabolism in these regions and the mood measures were also found. It is important to note that altered glucose metabolism in these regions may well be due to methamphetamine's impact on dopaminergic, as well as serotonergic, circuits (reviewed in the next section), which are strongly represented in these areas.

The evidence of methamphetamine's neurotoxic effect on neurochemistries involved in positive mood states (dopamine and serotonin), in conjunction with evidence of metabolic abnormalities in regions known to modulate mood states, indicates a fairly clear mechanism by which negative mood states result following prolonged use, and during withdrawal. This impact on mood is likely to occur regardless of premorbid mood states and predispositions, and should be an important consideration during management of cases of addiction.

Aggression and impulsivity

Deficits in emotional regulation are common in methamphetamine abusers, affecting not only control of depressive and anxious moods, but that of aggression and hostility as well (Payer, et al, 2008). Long-term use of methamphetamine has also been linked to elevated levels of impulsive behaviour (Semple et al, 2005), defined as the tendency to act without thinking and without regard for the negative consequences of an action for self or others (Moeller et al, 2001). Indeed, there are strong grounds for arguing that emotion dysregulation and impulsivity are strongly linked in methamphetamine abusers. This is consistent with evidence that methamphetamine intoxication is typically characterised by euphoric disinhibition (Meredith et al, 2005) and impaired decision-making (Payer et al,

2008). It also resonates with the finding that the inability to regulate both negative and positive mood states has been associated with increased impulsivity and substance use (Cyders & Smith, 2008).

One of the most problematic aspects of the interaction between emotion dysregulation and impulsivity in methamphetamine abuse is the increased tendency to commit acts of impulsive aggression. This may stem from the association between methamphetamine abuse and a reduced ability to regulate negative, hostile feelings and behaviours (Homer et al, 2008). Sommers et al (2006) found that 34.9% of methamphetamine abusers committed violent acts while under the influence of methamphetamine – almost half of these individuals had not demonstrated aggressive behaviour prior to abuse of this drug. In addition, Zweben et al (2004) observed that up to 43% of methamphetamine abusers reported difficulties in controlling violent behaviour. Visits to trauma centres following physical attacks are also more common in methamphetamine abusers than healthy controls, and they are more likely to be charged with assault, intentional injury, weapons possession and murder (Payer et al, 2008).

In fact, methamphetamine abuse is more strongly associated with violence than any other drug (Baicy & London, 2007). There is, moreover, evidence for the intergenerational transmission of antisocial behaviour following methamphetamine use. For instance, prenatal exposure to methamphetamines has been linked to increased aggression in 4–8-year-olds, as well as continuing problems in adolescence (Meredith et al, 2005). This is of particular concern for nations, such as South Africa, that are characterised by high background levels of violent crime, as it carries with it the spectre of continuing acts of aggressive behaviour in the future.

Poor emotional control, consistently identified in chronic users of methamphetamine, has been associated with abnormalities in functional and structural neuroanatomy. A complex network is thought to underlie emotion regulation, including the orbitofrontal cortex, anterior cingulate cortex and the amygdala. It is thought that an intact system features top-down control of emotional impulses originating in deeper brain structures. In the case of aggression, the orbitofrontal cortex and anterior cingulate are hypothesised to inhibit activation stemming primarily from the amygdala. Animal work and lesion studies support this view. Humans with damage to the orbitofrontal cortex frequently present with increased impulsivity and aggression. Marked deficits in moral reasoning and bursts of explosive anger have also been noted in these cases. A substantial body of work indicates that serotonergic dysfunction is implicated in individuals prone to impulsive violence (Davidson, Putnam & Larson, 2000).

The mechanisms whereby methamphetamine use may lead to increased impulsivity and aggressive behaviour have not been well researched in humans. However, animal studies on the neurotoxic effect of methamphetamine show clear damage to dopaminergic, as well as serotonergic, neurocircuitry (reviewed in Davidson et al, 2001). A recent human study, employing PET, found a significantly lower density of serotonin transporters in widespread regions of the brains of methamphetamine abusers, who also reported more aggressive behaviours than non-drug users (Sekine et al, 2006). In this study, more chronic methamphetamine use and increased aggression were associated with greater decreases in serotonin transporter density. Moreover, decreased serotonin transporter receptor density in

orbitofrontal, temporal and anterior cingulate cortex areas predicted aggression levels. This is consistent with evidence of a relationship between serotonergic activity and aggression in both the animal and human literature, and lends support to the model of impaired top-down regulation of aggressive impulses (Coccaro, 1996; Davidson et al, 2000).

Violent and aggressive behaviour is also associated with altered patterns of brain activation in abstinent methamphetamine-dependent patients. Hoffman and colleagues (2008), examining neural correlates of impulsivity in this population, found that methamphetamine abusers evidenced dysregulation in dorsal prefrontal and dorsal anterior cingulate regions thought to be critical in regulating impulsive behaviour. This is consistent with the conclusion in a recent review that aggressive behaviour and increased impulsivity may be influenced by impaired functioning of frontal regions of the brain caused by chronic exposure to methamphetamine (Homer et al, 2008). Further evidence stems from a PET study by Kim and colleagues (2005), in which a relationship was detected between the abnormally low metabolic rate of glucose in the frontal white matter of abstinent methamphetamine abusers and deficits in inhibiting impulsive acts. Nevertheless, despite the neurotoxicity of methamphetamine and the over-determined nature of the hostility and aggression associated with its use, not all users engage in aggressive behaviour.

Social behaviour

There is evidence that methamphetamine abuse may be characterised by deficits in social cognition and behaviour (Homer et al, 2008). Methamphetamine-induced psychotic symptoms in particular are associated with the tendency to misinterpret social situations and incorrectly attribute hostile intentions to others (Sommers et al, 2006). The study by Sommers et al (2006) described earlier found paranoia to be a relatively frequent consequence of methamphetamine abuse; 62% in a sample of 106 abusers experienced paranoia, with fear of others being reported most frequently. It seems likely that this psychotic symptom is associated with the attribution of hostile intentions to others, particularly in a population characterised by deficits in emotion recognition and empathy (described below), increasing the chances that misinterpreted situations will lead to violence. This is especially probable as these features occur in combination with poor affect regulation and impulse control, leading to the situation in which everyday interactions trigger violence through the unregulated anger elicited by perceived violations of personal codes like respect and personal space (Sommers et al, 2006). Paranoid attributions, emotion dysregulation and the resulting aggressive behaviour may therefore underlie the high rates of violence, physical and sexual abuse associated with the abuse of methamphetamines (Baicy & London, 2007).

A particular deficit in social-cognitive function associated with methamphetamine abuse is difficulty in recognising emotions in other people. For instance, in a recent study employing a facial affect recognition task, methamphetamine abusers demonstrated difficulties in identifying six basic emotions (anger, fear, happiness, sadness, surprise and disgust) (Henry, Mazur & Rendell, 2009). Although Payer et al (2008) was not able to replicate these findings with respect to the recognition of fearful and angry faces in a group of 12 abstinent (5–16 days) methamphetamine abusers and healthy participants, there were differences between the groups in the activation of cortical regions linked to processing

affective and social cognitive information. Specifically, less task-related activity was observed in methamphetamine abusers in the ventrolateral prefrontal cortex, implicated in affect processing, as well as in the anterior and posterior temporal cortex and the temporoparietal junction, regions thought to be involved in social cognition. In contrast, higher task-related activity was observed in this group in the dorsal anterior cingulate cortex, an area of the brain implicated in forms of social hyperactivity that can lead to aggressive behaviour (Eisenberger et al, 2007). These findings, in combination with reports of high self-ratings of hostility among methamphetamine abusers, suggest a hypersensitivity to socially threatening cues in this population (Payer et al, 2008).

Another important aspect of social-cognitive function which may be disrupted by methamphetamine abuse is 'Theory of Mind'. This is the ability to quickly and accurately infer people's mental states, such as intentions, beliefs and desires (Premack & Woodruff, 1978). Being able to see things from another person's perspective constitutes an important basis for empathy and social communication. Performance on Theory of Mind (TOM) tasks therefore can be interpreted as a measure of social competence. One of the most commonly employed TOM tasks is the 'Reading the Mind in the Eyes' test (Baron-Cohen et al, 2001), which requires recognition of affective states from images of eyes only. The test differs from basic facial affect recognition tasks in that the discrimination of affective states involves more complex emotional terms and often concerns social interaction (Henry et al, 2009).

To date, a single study has employed the Reading the Mind in the Eyes test to assess the effects of methamphetamines on complex emotional processing. Henry et al (2009) compared the performance of 12 methamphetamine abusers who had been in rehabilitation and abstinent on average for 6 months with that of healthy controls. Performance deficits were observed in the methamphetamine abusers relative to the healthy controls, suggesting that methamphetamine abuse leads to multiple potentially chronic forms of social-cognitive impairment. In a review by Frith and Frith (2003) three regions that show selective activation during Theory of Mind tasks were identified: the medial prefrontal cortex, the temporal lobes and the posterior superior temporal sulcus. Impaired functioning in these brain regions has been observed in methamphetamine abusers, potentially explaining deficits in social-cognitive functioning in this population (Homer et al, 2008).

In conclusion, difficulties among methamphetamine abusers (abstinent and current) in the correct identification of basic as well as socially complex emotions in other people, as evidenced by damage in this group to neural circuitry thought to be crucial to these abilities, may constitute vulnerability factors for engaging in contextually inappropriate behaviours, thereby leading to increased levels of social conflict.

Conclusion

Affective neuroscience is able to articulate the neurochemical and neurophysiological underpinnings of the changes in mood and behaviour seen in methamphetamine abusers. It has been demonstrated that the neurotoxic effects of methamphetamine result in both acute and more long-term changes to key neurocircuitries involved in reward processing and affect regulation. Changes in dopaminergic function appear to result in alterations in

reward sensitivity characterised by reduced ability to experience positive hedonic states for various natural rewards, while simultaneously increased drug intake is required to achieve rewarding, and to avoid aversive, mood states. Dysregulation of serotonergic function also contributes to deficits in frontally mediated affect and impulse regulation, and these neurochemical changes may underlie the marked increase in impulsive aggression seen in many methamphetamine abusers.

Methamphetamine abuse is also associated with altered function in key regions associated with social function, in conjunction with deficits in the ability to recognise basic and more complex mental states in others. This deficit in social cognition, alongside possible increases in paranoia, is thought to contribute to the misattribution of hostile intentions to others, which may then rapidly result in conflictual situations and aggression, due to impaired regulation of aggressive impulses.

Several shortcomings are present in the literature on the affective neuroscience of methamphetamine abuse. Firstly, cross-sectional and retrospective designs are most often used, which results in several problems when interpreting data. In cross-sectional designs it is difficult to determine causal relationships between methamphetamine abuse and behavioural, as well as neural structural and functional changes. Some researchers (eg, Berman et al, 2008; Lin et al, 2004) use retrospective designs, where associations are found between methamphetamine use and psychiatric disorders or structural changes in the brain. The difficulty here lies in clarifying whether disorders such as depression or psychosis are predisposers to, rather than consequences of, methamphetamine abuse.

Another potential confound is the failure to properly characterise various drug use parameters. Research in this area does not generally control for possible dose-dependent effects of abuse on brain structure and functioning, with many researchers combining data from participants with varying levels of methamphetamine abuse. The observation that methamphetamine users frequently abuse other drugs as well, including alcohol (Lin et al, 2004), nicotine and opioids such as heroin (Williams, Christie & Manzoni, 2001), is also generally not considered. These drugs may have additive or interactive effects on behaviour and neural structure and function. Future research should employ study designs (ie, longitudinal studies) and data analysis strategies that are better able to control for the effects of comorbid drug use and psychopathology .

Another difficulty lies in differentiating the effects of methamphetamine at the different stages of use, withdrawal and abstinence. The immediate effects of methamphetamine on brain functioning and metabolism are likely to be very different to the long-term effects of the drug, judging by the observed behavioural tendencies of methamphetamine intoxication versus withdrawal. This problem is compounded by the recognition that abstinence itself may not be a homogenous state. Studies that have used participants at various stages of abstinence have frequently obtained different results for affective behaviour, as well as brain structure and functioning. These variations suggest that abstinence is not a unitary state, but rather an ongoing process of recovery or enduring pathology. Yet much research has used abstinent participants as an undifferentiated group, without controlling for time since last intake of methamphetamine.

These effects of individual differences in stage of abuse or drug use parameters are difficult to isolate, given the small samples that are invariably employed in studies in this

area. Recruiting large samples is understandably difficult with clinical populations, and this problem intensifies when the population studied may be reluctant to participate in research due to legal ramifications and the social stigma that surrounds their drug habit. The logistic and financial constraints imposed by imaging research also contribute to the small sample sizes commonly reported. Future multi-site collaborative research initiatives are required in order to generate the sample sizes needed to address these issues.

As a general critique of the neuroscience literature in this area, there is a lack of data on the affective consequences of methamphetamine abuse, in comparison to the relatively clear delineation of cognitive deficits. Although the discipline of affective neuroscience is still in its infancy, it has much to offer to the field. The most pressing aspects of the problem of methamphetamine abuse, namely, high rates of violence and antisocial behaviour, have an affective dimension. More research is needed to understand the extent to which this aggression and violence results from neurochemical changes caused by methamphetamine abuse, and in what ways these intra-individual changes interact with macro-level socio-political phenomena, such as inequality and gangsterism.

There are clear indications that affect regulation, impulse control and social cognition are adversely affected by methamphetamine abuse, and the literature is able to provide some explanation of how these deficits are enacted at a neural and neurochemical level. However, our opinion is that the current state of knowledge regarding the neuroscience of affect in methamphetamine abuse is suggestive rather than definitive, and that ongoing work in this area is urgently required to build a more solid knowledge base.

References

Alcaro, A., Huber, R. & Panksepp, J. (2007). Behavioral functions of the mesolimbic dopaminergic system: an affective neuroethological perspective. *Brain Research Reviews*, 56(2):283–321.

Baicy, K. & London, E.D. (2007). Corticolimbic dysregulation and chronic methamphetamine abuse. *Addiction*, 102(1):5–15.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y. & Plumb, I. (2001). The 'Reading the Mind in the Eyes' test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 42(2):241–51.

Berman, S., O'Neill, J., Fears, S., Bartzokis, G. & London, E.D. (2008). Abuse of amphetamines and structural abnormalities in the brain. *Annals of the New York Academy of Sciences*, 1141(Addiction Reviews 2008):195–220.

Coccaro, E.F. (1996). Neurotransmitter correlates of impulsive aggression in humans. *Annals of the New York Academy of Sciences*, 794(1):82–89.

Cyders, M.A. & Smith, G.T. (2008). Emotion-based dispositions to rash action: positive and negative urgency. *Psychological Bulletin*, 134(6):807–28

Davidson, C., Gow, A.J., Lee, T.H. & Ellinwood, E.H. (2001). Methamphetamine neurotoxicity: necrotic and apoptotic mechanisms and relevance to human abuse and treatment. *Brain Research Reviews*, 36(1):1–22.

Davidson, R.J., Putnam, K.M. & Larson, C.L. (2000). Dysfunction in the neural circuitry of emotion regulation: a possible prelude to violence. *Science*, 289(5479):591–94.

Eisenberger, N.I., Way, B.M., Taylor, S.E., Welch, W.T. & Lieberman, M.D. (2007). Understanding genetic risk for aggression: clues from the brain's response to social exclusion. *Biological Psychiatry*, 61(9):1100–108.

Frith, U. & Frith, C.D. (2003). Development and neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 358(1431):459–73.

Henry, J.D., Mazur, M. & Rendell, P.G. (2009). Social-cognitive difficulties in former users of methamphetamine. *British Journal of Clinical Psychology*, 48(2):323–27.

Hoffman, W.F., Schwartz, D.L., Huckans, M.S., McFarland, B.H., Meiri, G., Stevens, A.A. & Mitchell, S.H. (2008). Cortical activation during delay discounting in abstinent methamphetamine dependent individuals. *Psychopharmacology*, 201(2):183–93.

Homer, B.D., Solomon, T.M., Moeller, R.W., Maxcia, A., DeRaleau, L. & Halkitis, P.N. (2008). Methamphetamine abuse and impairment of social functioning: a review of the underlying neurophysiological causes and behavioral implications. *Psychological Bulletin*, 134(2):301–10.

Hyman, S.E. (2005). Addiction: a disease of learning and memory. *American Journal of Psychiatry*, 162:1414–22.

Kim, S.J., Lyoo, I.K., Hwang, J., Sung, Y.H., Lee, H.Y., Lee, D.S., Jeong, D.U. & Renshaw, P.F. (2005). Frontal glucose hypometabolism in abstinent methamphetamine users. *Neuropsychopharmacology*, 30(7):1383-91.

Koob, G.F. (2009). Dynamics of neuronal circuits in addiction: reward, antireward, and emotional memory. *Pharmacopsychiatry*, 42(Suppl. 1):S32–S41.

Lin, S., Ball, D., Hsiao, C., Chiang, Y., Ree, S. & Chen, C. (2004). Psychiatric comorbidity and gender differences of persons incarcerated for methamphetamine abuse in Taiwan. *Psychiatry and Clinical Neurosciences*, 58(2):206–12.

London, E.D., Simon, S.L., Berman, S.M., Mandelkern, M.A., Lichtman, A.M., Bramen, J., Shinn, A.K., Miotto, K., Learn, J., Dong, Y., Matochik, J.A., Kurian, V., Newton, T., Woods, R., Rawson, R. & Ling, W. (2004). Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. *Archives of General Psychiatry*, 61(1):73–84.

McCann, U.D., Wong, D.F., Yokoi, F., Villemagne, V., Dannals, R.F. & Ricaurte, G.A. (1998). Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [11C] WIN-35,428. *Journal of Neuroscience*, 18(20):8417–22.

Meredith, C.W., Jaffe, C., Ang-Lee, K. & Saxon, A.J. (2005). Implications of chronic methamphetamine use: a literature review. *Harvard Review of Psychiatry*, 13(3):141–54.

Moeller, F.G., Dougherty, D.M., Barratt, E.S., Schmitz, J.M., Swann, A.C. & Grabowski, J. (2001). The impact of impulsivity on cocaine use and retention in treatment. *Journal of Substance Abuse Treatment*, 21(4):193–98.

Obot, I.S., Poznyak, V. & Monteiro, M. (2004). From basic research to public health policy: WHO report on the neuroscience of substance dependence. *Addictive Behaviours*, 29(7):1497–502.

Panksepp, J. (2005). Affective consciousness: core emotions in animals and humans. *Consciousness and Cognition*, 14(1):30–80.

Payer, D.E., Lieberman, M.D., Monterosso, J.R., Xu, J., Fong, T.W. & London, E.D. (2008). Differences in cortical activity between methamphetamine-dependent and healthy individuals performing a facial affect matching task. *Drug and Alcohol Dependence*, 93(1–2):93–102.

Plüddemann, A., Myers, B. & Parry, C. (2009). *Fact Sheet – Methamphetamine*. Alcohol and Drug Abuse Research Unit, Medical Research Unit, Medical Research Council.

Premack, D.G. & Woodruff, G. (1978). Does the chimpanzee have a theory of mind? *Behavioral and Brain Sciences*, 1(4):515–26.

Sarkar, M. & Kornetsky, C. (1995). Methamphetamine's action on the brain stimulation reward threshold and stereotypy. *Experimental and Clinical Psychopharmacology*, 3(2):112–17.

Saunders, C., Ferrer, J.V., Shi, L., Chen, J., Merrill, G., Lamb, M.E., Leeb-Lundberg, L.M.F., Carvelli, L., Javitch, J. & Galli, A. (2000). Amphetamine-induced loss of human dopamine transporter activity: an internalization-dependent and cocaine-sensitive mechanism. *Proceedings of the National Academy of Sciences*, 97(12):6850–55.

Sekine, Y., Iyo, M., Ouchi, Y., Matsunaga, T., Tsukada, H., Okada, H., Yoshikawa, E., Futatsubashi, M., Takei, N. & Mori, N. (2001). Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. *American Journal of Psychiatry*, 158(8):1206–14.

Sekine, Y., Minabe, Y., Ouchi, Y., Takei, N., Iyo, M., Nakamura, K., Suzuki, K., Tsukada, H., Okada, H., Yoshikawa, E., Futatsubashi, M. & Mori, N. (2003). Association of dopamine transporter loss in the orbitofrontal and dorsolateral prefrontal cortices with methamphetamine-related psychiatric symptoms. *American Journal of Psychiatry*, 160(9):1699–701.

Sekine, Y., Ouchi, Y., Takei, N., Yoshikawa, E., Nakamura, K., Futatsubashi, M., Okada, H., Minabe, Y. Suzuki, K., Iwata, Y., Tsuchiya, K.J., Tsukada, H., Iyo, M. & Mori, N. (2006). Brain serotonin transporter density and aggression in abstinent methamphetamine abusers. *Archives of General Psychiatry*, 63(1):90–100.

Semple S.J., Zians J., Grant I. & Patterson T.L. (2005). Impulsivity and methamphetamine use. *Journal of Substance Abuse Treatment*, 29(2):85–93.

Sommers, I., Baskin, D.R. & Baskin-Sommers, A. (2006). Methamphetamine use among young adults: health and social consequences. *Addictive Behaviors*, 31(8):1469–76.

Sulzer, D., Sonders, M.S., Poulsen, N.W. & Galli, A. (2005). Mechanisms of neurotransmitter release by amphetamines: a review. *Progress in Neurobiology*, 75(6):406–33.

Thompson, P.M., Hayashi, K.M., Simon, S.L., Geaga, J.A., Hong, M.S., Sui, Y., Lee, J.Y., Toga, A.W., Ling, W. & London, E.D. (2004). Structural abnormalities in the brains of human subjects who use methamphetamine. *Journal of Neuroscience*, 24(26):6028–36.

Villemagne, V., Yuan, J., Hatzidimitriou, G., Mathews, W., Ravert, H.T., Musachio, J., McCann, U.D. & Ricuarte, G.A. (1998). Brain dopamine neurotoxicity in baboons treated with doses of methamphetamine comparable to those recreationally abused by humans: evidence from [11C]WIN-35,428 positron emission tomography studies and direct *in vitro* determinations. *Journal of Neuroscience*, 18(1):419–27.

Volkow, N.D., Chang, L., Wang, G.-J., Fowler, J.S., Ding, Y.-S., Sedler, M., Logan, J., Franceschi, D., Gatley, J., Hitzemann, R., Gifford, A., Wong, C. & Pappas, N. (2001). Low level of brain dopamine D(2) receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *American Journal of Psychiatry*, 158(12):2015–21.

Volkow, N.D., Fowler, J.S., Wang, G.J. & Goldstein, R.Z. (2002). Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. *Neurobiology of Learning and Memory*, 78(3):610–24.

Volkow, N.D., Wang, G-J., Fowler, J.S., Logan, J., Gatley, S.J., Wong, C., Hitzemann, R. & Pappas, N.R. (1999). Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D2 receptors. *Journal of Pharmacology and Experimental Therapeutics*, 291(1):409–15.

Völlm, B.A., De Araujo, I.E., Cowen, P.J., Rolls, E.T., Kringelbach, M.L., Smith, K.A., Jezzard, P., Heal, R.J. & Matthews, P.M. (2004). Methamphetamine activates reward circuitry in drug naive human subjects. *Neuropsychopharmacology*, 29:1715–22.

Watanabe-Galloway, S., Ryan, S., Hansen, K., Hullsiek, B., Muli, V. & Malone, C. (2009). Effects of methamphetamine abuse beyond individual users. *Journal of Psychoactive Drugs*, 41(3):241–48.

Williams, J.T., Christie, M.J. & Manzoni, O. (2001). Cellular and synaptic adaptations mediating opioid dependence. *Physiological Reviews*, 81(1):299–343.

Zweben, J., Cohen, J., Christian, D., Galloway, G.P., Salinardi, M., Parent, D., Iguchi, M.; Methamphetamine Treatment Project. (2004). Psychiatric symptoms in methamphetamine users. *American Journal on Addictions*, 13(2):181–90.

9 Neurocognitive effects of alcohol abuse and dependence

Kevin G.F. Thomas and Helen L. Ferrett

Introduction

As other chapters in this volume have highlighted, alcohol is the most frequently abused substance in the Western Cape, as well as the most common primary substance of abuse presenting at clinics, hospitals, and other treatment sites nationwide (Parry et al, 2005; Plüddemann et al, 2009). Furthermore, neuropsychologists in this country frequently encounter psychiatric and neurological disorders directly and indirectly related to chronic alcohol use. For instance, the prevalence of fetal alcohol spectrum disorders (FASD) in South Africa is among the highest in the world (May et al, 2007; Urban et al, 2008) (see Chapter 3), suggesting that even pregnant women in certain local communities use alcohol to troubling degrees.

Our review focuses largely on ways in which heavy drinking affects performance within particular domains of cognitive functioning (especially executive functioning). We touch on factors that moderate or mediate the effects of alcohol on neuropsychological functioning, and consider ways in which cognitive performance improves after a period of abstinence. To conclude the chapter, we discuss some of our own work on the neuropsychological performance of South African alcohol-dependent adolescents.

Neuropsychological sequelae of chronic alcohol use

The literature we review is focused on individuals with alcohol-use disorders (AUD). The term 'AUD' refers to the collection of symptoms present in persons carrying DSM-IV diagnoses of alcohol dependence or alcohol abuse, or ICD-10 diagnoses of dependence or harmful use (Grant et al, 2004; Schuckit, 2009) (see Chapter 2). Furthermore, as in many other such reviews, we concentrate on 'uncomplicated' AUD (that is, AUD with no history of Wernicke-Korsakoff syndrome or of chronic hepatic disease), given that this category represents most individuals with alcohol-use disorders (Durazzo & Meyerhoff, 2007).

Although the precise mechanisms underlying the effects of alcohol on the brain are beyond the scope of this chapter (and, indeed, are still the subject of some debate in the literature), it is useful to note that brain regions particularly vulnerable to the neurotoxic effects of chronic alcohol use include the frontal lobes, the limbic system (including the hippocampus, amygdala and hypothalamus) and the cerebellum (Oscar-Berman & Marinkovic, 2007). Damage to these structures is probably responsible for the typical neuropsychological profile observed in individuals with AUD: a scattered pattern of strengths and weaknesses across cognitive domains, with language, verbal abilities and IQ remaining relatively intact, while information

processing speed, complex perceptual-motor integration, visuospatial abilities, learning, episodic memory, working memory and, particularly, executive skills are impaired (eg, Bates et al, 2002; Beatty et al, 1996; Grant, 1987; Parsons et al, 1987; Pitel et al, 2007).

Although several of the basic and most frequently cited studies on cognitive impairment associated with AUD were published as many as 30 years ago, researchers continue to refine questions related to, and methods and tools to explore, neuropsychological deficits in heavy drinkers. For instance, Green et al (2010) noted that, even in treatment-seeking individuals who are most severely affected and who therefore would be expected to show quite significant signs of cognitive impairment (Fein et al, 2002), neuropsychological assessments often fail to detect any such impairment. Given that one probable reason for this failure is that the neuropsychological instruments being used are not appropriate for the purpose of detecting impairment in AUD individuals, Green and colleagues set out to test the clinical utility of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al, 1998) for that population.

The RBANS has been established as an effective screening tool for use in several different clinical populations (eg, Hook et al, 2010; Larson et al, 2005; Wilk et al, 2002), and is considered particularly suitable as a screen because administration time is short (20–30 minutes), scoring is easy and interpretation is relatively simple. Furthermore, the instrument delivers separate scores on many essential cognitive domains, including verbal and visual memory, language, attention and visuospatial abilities (Duff et al, 2003; Gontovksy et al, 2004). Most significantly for the South African clinical neuropsychologist, and the reason we are highlighting the work by Green et al (2010) on the use of this instrument in the assessment of heavy drinkers, is the fact that the RBANS has demonstrated utility in cross-cultural neuropsychological assessment (Lim et al, 2010; Patton et al, 2003). The practice of clinical neuropsychology in South Africa is severely hamstrung by the lack of culturally appropriate instruments that are properly standardised and normed (Nell, 2000; Shuttleworth-Jordan, 1996). The availability of a screening instrument with the psychometric and cross-cultural properties of the RBANS is therefore important to note.

Green et al (2010) compared a group of moderate-to-heavy drinkers (n = 28, intake of 30–80 g of ethanol per day) to a demographically matched control group (n = 28, intake of <21 g of ethanol weekly). Consistent with predictions based on previous literature, participants in the alcohol group performed more poorly on measures of new learning and memory and visuospatial ability, but were intact on measures of basic attention and language. Although these data do not add any particularly new insights into the neuropsychological profile of AUD individuals, their value is in the fact that they (1) are derived from a screening battery of co-normed subtests covering most major domains of cognitive function, and yet still (2) confirm previously established patterns of performance.

Executive functioning in AUD individuals

The concept of a 'central executive' responsible for the general organisation of behaviour was introduced by Baddeley and Hitch (1974). Subsequent theoretical and empirical work has expanded upon that concept, so that 'executive functions' are now defined as encompassing several components, including the ability to form goals, plan a means to attain those goals, execute those plans and self-monitor progress toward the goals so as to adapt the plan to

environmental contingencies (Lezak et al, 2004). Intact executive functioning is therefore essential for 'appropriate, socially responsible and effectively self-serving adult conduct' (Jurado & Rosselli, 2007:213).

Neural circuitry within, and connected to, the frontal lobes subserves the executive functions. As other chapters in this volume (particularly Malcolm-Smith et al and Meintjes et al) have emphasised, there is converging evidence from basic and clinical research, using neuroimaging, psychophysiological and neuropathological techniques, that substances of abuse selectively target neural circuits and neurotransmitter systems centred on and interacting with the frontal lobes (Sullivan, 2007). Although those chapters focused on methamphetamine, the same circuits and systems, and thus the same frontal regions, are also especially vulnerable to the effects of alcohol abuse and dependence (Moselhy et al, 2001, Oscar-Berman & Marinkovic, 2007). For instance, neuropathological work by Harper and colleagues (1985, 1998, 2005) on the brains of deceased alcoholics showed selective neuronal loss from the frontal cortical regions. Early structural MRI studies revealed associations between alcohol consumption and volume losses in the frontal lobes (Pfefferbaum et al, 1997). More recently, a diffusion tensor MRI study confirmed associations between diminished white matter integrity in the right hemisphere frontal regions (superior longitudinal fascicles, orbitofrontal cortex and cingulum) and performance on tests of working memory (Harris et al, 2008). Similarly, functional MRI studies using both adolescent and adult AUD participants have revealed abnormalities in frontal activation during engagement in working memory tasks (Tapert, Pulido et al, 2004; Tapert, Shweinsburg et al, 2004; Vollstadt-Klein et al, 2010), and a PET study showed hypometabolism in the mediofrontal cortex, which was positively correlated with reduced verbal generativity, and in the left dorsolateral prefrontal cortex, which was positively correlated with reduced behavioural inhibition (Dao-Castellana et al, 1998).

Although the basic and clinical science work reviewed above is elegant and highly informative, until relatively recently a problem for clinicians who needed to document, via neuropsychological assessment, the association between chronic alcohol consumption and frontal dysfunction was that such assessment of frontal lobe functioning was notoriously difficult. In his classic paper, Teuber (1964) referred to the 'recurrent perplexity' inherent in the fact that '[m]an's frontal lobes have always presented problems that seemed to exceed those encountered in studying other regions of his brain' (p. 410). One of the problems Teuber sought to highlight was that patients with frontal damage presented in such varying ways that attempts to describe a consistent frontal pathology were frustrating to the neurologists, psychophysiologists and physicians of his day. Over the past several decades, of course, advances in electrophysiological and *in vivo* neuroimaging techniques, as well as more careful experimental approaches to lesion studies, have allowed neuropsychologists and cognitive neuroscientists to unravel Teuber's riddle, and to delineate in reasonable detail the functional neuroanatomy of the frontal lobes (Bigler, 2009; Mega & Cummings, 1994; Stuss & Levine, 2002).

Of course, these advances have offered research and clinical neuropsychologists tools that are better able to measure discrete executive functions, such as attentional control, verbal fluency, planning, set-shifting, goal-setting, problem-solving, cognitive flexibility, inhibition and impulse control, and their association with discrete frontal circuitry. Those

neuropsychologists assessing AUD patients have benefited as much as anyone from these tools, and, over the last two decades, a sizeable literature examining discrete executive functioning deficits in AUD individuals has emerged. In general, this literature suggests that chronic consumption of alcohol over a lengthy period is associated with deficits in abstract thinking, cognitive flexibility and the ability to persist with a certain set of successful responses while inhibiting competing intrusive impulses (Moselhy et al, 2001; Noel et al, 2001; Ratti et al, 2002).

For instance, in a wide-ranging investigation, Ihara et al (2000) found that their group of 17 alcohol-dependent individuals performed more poorly than matched controls on tests of everyday problem-solving, concept formation, set-shifting and behavioural inhibition, even though they showed no deficits on tests of memory or general intellectual functioning. Similarly, Zago-Gomes and Nakamura-Palacios (2009) used a brief bedside screening battery (the Frontal Assessment Battery, or FAB) sensitive to executive dysfunction (Dubois et al, 2000) in their study of 170 Brazilian alcohol-dependent outpatients. They found that, compared to non-alcoholic controls, the patients performed more poorly on FAB measures of motor programming, sensitivity to interference and inhibitory control.

In studies measuring only one specific executive function, alcohol-dependent individuals performed more poorly on the Iowa Gambling Task, an instrument which assesses decision-making and is sensitive to lesions of the ventromedial prefrontal cortex (Bechara et al, 2001; Mazas et al, 2000). Similarly, Nixon and Parsons (1991) showed that alcoholics completing a nonverbal abstraction task did not score any differently from a non-alcoholic control group when only their final answers were examined, but that alcoholics were less efficient in solving the problems. This relative lack of problem-solving efficiency was also identified by Fama et al (2004), who showed that alcoholics recruited executive systems to help them solve perceptual learning problems, whereas non-alcoholic controls used only basic visuospatial processes to complete the same set of problems (see also Glenn & Parsons, 1991, 1992; Nixon et al, 1995).

Because deficits in executive functioning are, in general and in AUD, so often associated with personality and behavioural dysfunction (Finn et al, 2000, 2009; Lezak et al, 2004; Mazas et al, 2000; Oscar-Berman & Marinkovic, 2007), much of the recent literature on executive impairment in AUD has sought to investigate questions such as whether the extent of such impairment is predictive of treatment outcome or of the ability to abstain from alcohol (Goldstein & Volkow, 2002; Moselhy et al, 2001). Although cognitive impairment in general is negatively associated with (1) positive prognosis following treatment and (2) ability to acquire treatment-relevant information successfully (Godding et al, 1992; Parsons, 1983; Smith & McCrady, 1991), specific executive function impairments in AUD individuals are even more likely to affect the course and success of rehabilitation attempts. For instance, Teichner and colleagues (2001) reported that successful attainment of treatment objectives by patients enrolled in a comprehensive rehabilitation programme was related to pre-intervention performance on a working memory task. Miller (1991) reported that impaired abstract thinking ability, cognitive flexibility, planning and behavioural inhibition were more prevalent in relapsers than in successful recoverers.

It is clear, therefore, that there is an association between executive dysfunction and treatment failure/relapse. What is not clear are the mechanisms underlying that association.

As Blume and Marlatt (2009) state, it is likely that these mechanisms are much more complex than simply asserting that, for instance, impaired behavioural inhibition leads to an inability to abstain from alcohol or to avoid alcohol-related settings. Although few published studies directly address these complexities, some suggest that the relationship between executive dysfunction and poor treatment outcome might be mediated by the presence of impairments in particular functional domains, such as the marital relationship (Tuck & Jackson, 1991) and employment status (Moriyama et al, 2002).

Individual differences in the effects of alcohol on neurocognition

Our review to this point has implied, somewhat misleadingly, that there is a typical AUD individual with a typical profile of alcohol-induced neuropsychological impairment. In fact, the nature, pattern, and degree of impairment vary across individuals, probably because there are individual differences in the location and extent of alcohol-related neural injury (Oscar-Berman & Marinkovic, 2007). For instance, data from family, twin and adoption studies converge to suggest that vulnerability to alcohol abuse and dependence, as well as metabolic responses to alcohol, are quite strongly influenced by hereditary factors and genetic variants (Begleiter & Porjesz, 1999; Dick & Foroud, 2003; Edenberg & Foroud, 2006). Demographic variables (eg, age, sex, education) also moderate the relationship between alcohol use and AUD-induced neurobiological and neuropsychological impairment. Similarly, polysubstance use, poor nutrition and comorbid psychiatric and neurological conditions can exacerbate the effects of alcohol on the brain, and can create environmental circumstances under which the individual's intake of alcohol increases (Oscar-Berman & Marinkovic, 2003; Petrakis et al, 2002).

The factors listed above are, somewhat surprisingly, stronger predictors of neuropsychological impairment in abstinent alcoholics than are alcohol-use patterns (eg, duration of use, type and typical amount consumed; Adams & Grant, 1984; Fein et al, 1990). It is important that clinical neuropsychologists bear this point in mind during history-taking when assessing an AUD individual, and it is for this reason that we review in more detail two of the moderating variables listed above: sex and age.

Over the past 20 years, the literature on sex differences in the effects of chronic AUD on brain structure and function has grown remarkably. Despite this increasing interest, neuroimaging studies have come no closer to confirming with any consistency that either male or female alcoholics are more susceptible than the opposite sex to reduced grey or white matter changes in brain metabolism, or variations in task-related neural activity (see Oscar-Berman & Marinkovic, 2007, for a review).

Similarly, studies of sex differences in neuropsychological performance of AUD individuals have delivered contradictory evidence. For instance, a recent cross-sectional study of alcohol-dependent Russian adults found that females performed more poorly than males on tests of cognitive flexibility, visuospatial processing and problem-solving (Flannery et al, 2007). These data are not consistent with those presented by Yonker et al (2005), who showed that, in men and women aged between 35 and 85 years, only groups classified as non-drinkers or light drinkers showed sex differences in favour of men on visuospatial tasks. Yonker and colleagues also showed, however, that women outperformed men on an episodic memory task across all levels of alcohol consumption. These data, in turn, are not

consistent with those presented by Sullivan and colleagues (2000b, 2002), who showed that, relative to non-alcoholic matched controls, both alcoholic men and women showed preserved declarative memory functioning. One of the results presented by Sullivan et al (2002) has been replicated in a recent study, however: in a sample of alcohol-dependent Taiwanese individuals, women performed more poorly than men on measures of working memory (Liu et al, 2010).

The data with regard to the moderating effects of age on AUD-induced neuropsychological impairment are much more unambiguous than those with regard to sex differences. In healthy, non-alcoholic individuals, age-related changes in neuroanatomy, neurophysiology and neurochemistry are similar to changes observed in the brains of alcoholic individuals. For instance, processes such as ventriculomegaly (widening of, in particular, the lateral ventricles), frontal and cerebellar atrophy and enlargement of the cerebral sulci are observed in normal ageing brains as well as in alcoholic brains (see, eg, Harper, 1998; Makris et al, 2008; Pfefferbaum et al, 1997; Sullivan et al, 2000). Furthermore, as people age they show a marked increase in physiological sensitivity to alcohol (Dufour & Fuller, 1995; Meier & Seitz, 2008; Pozzato et al, 1995; Spencer & Hutchinson, 1999).

These neurobiological observations led to the formulation of a theoretical framework, the premature ageing hypothesis, which attempted to describe and predict analogous AUD- and age-related cognitive changes. In its most empirically viable form, this model postulates that

> an aging brain is more vulnerable to the influences of toxic substances, including ethanol, than is the brain of a younger person … [and therefore] only older alcoholics (over age 50) are [cognitively] impaired compared with age-matched controls; younger alcoholics remain cognitively intact. (Oscar-Berman & Marinkovic, 2007:240)

Cross-sectional neuroimaging and neuropathological studies, comparing younger to older AUD individuals, have provided evidence confirming this proposition: cortical, subcortical and cerebellar brain regions, as well as the corpus callosum, are smaller and feature reduced blood flow in older, compared to younger, alcoholics (see Oscar-Berman & Marinkovic, 2007, for a review). Furthermore, the extent of these specific neuroanatomical and neurochemical changes in the brains of ageing alcoholics correlates strongly with the extent of specific neuropsychological changes (particularly in the domains of working memory, processing speed and visuospatial abilities) and of specific psychomotor changes (as measured, for example, by gait and balance composites) manifested by those individuals (Pfefferbaum et al, 2006; Schulte et al, 2005; Sullivan et al, 2000b).

Improvement with abstinence

Clinical neuropsychologists working in rehabilitation and treatment settings will typically assess AUD individuals at baseline (ie, upon admission to the rehabilitation/treatment programme) and then again several months later (either after completion of the entire programme or at an appropriately spaced interval within the programme). A key question the clinician faces at follow-up assessment is whether he/she should expect to see any recovery of cognitive function in the now-abstinent AUD individual.

The literature regarding reversibility of AUD-induced neural damage provides some answers to this question. Neuroimaging studies suggest there is no difference in global cerebral atrophy between older abstinent men and matched controls (Di Sclafani et al, 1995), that there is evidence of at least partial recovery of metabolic function and of region-specific recovery of white-matter volume in long-term abstinent individuals (Johnson-Greene et al, 1997; O'Neill et al, 2001), and that reversibility of ventricular enlargement can be achieved with even short-term abstinence (Zipursky et al, 1989). Although not all of these (and other similar) neuroimaging studies measured cognitive function and correlated it with abstinence-associated structural/metabolic changes, of those that did, most found that underlying brain changes were mirrored by changes in performance on neuropsychological tests.

There are, however, other important factors for the neuropsychologist to consider when conducting post-treatment or post-abstinence assessments. The individual differences noted above are again critical. For instance, Rourke and Loberg (1996) report that after two to three weeks of abstinence 45% of alcoholics continue to show detectable neuropsychological impairment; after one year of abstinence, 15% continue to show such deficits. The implication here is that the same moderating/mediating variables listed in the previous section impact upon the magnitude and trajectory of recovery following a period of abstinence (Rourke & Grant, 1999; Skinner et al, 1989; Solomon & Malloy, 1992).

In general, however, there is improvement (and sometimes even as much as a return to normal levels) in numerous domains of cognitive functioning after both short (one to three months) and longer (more than 12 months) periods of abstinence (see Durazzo & Meyerhoff, 2007, and Moselhy et al, 2001, for reviews). For instance, performance on tests of psychomotor functioning, attention, working memory, associative learning, visual memory, verbal declarative memory, visuospatial abilities and fund of verbal knowledge improves with prolonged abstinence (Brandt et al, 1983; Reed et al, 1992; Rourke & Grant, 1999). Furthermore, some studies (eg, Mann et al, 1999; Sullivan et al, 2000b) suggest that recovery occurs within weeks when complete abstinence is maintained.

With regard to AUD-induced impairments in executive functioning, although there is something of a lack of systematic investigation, the trajectory of recovery following abstinence appears to be less clear-cut than that for other cognitive abilities. Moselhy et al (2001:365) suggest in their review that 'frontal lobe changes are potentially reversible to some degree with abstinence for several months or years, but even after several years the brain may remain abnormal'. Data from numerous neuropsychological studies are consistent with this suggestion, showing that deficits in abstract reasoning, behavioural inhibition, planning, verbal generativity and cognitive flexibility can persist (Bates et al, 2005; Clarke & Haughton, 1975; Munro et al, 2000; Zinn et al, 2004), even after long periods of abstinence (Fein et al, 1990; Medina et al, 2004; although see Fein & McGillivray, 2007, for contradictory data).

Adolescent alcohol abusers in South Africa: neuropsychological findings

Almost all of the literature reviewed above, and by far the majority of the literature in the field, focuses on adults with AUD. Local and international developmental studies of alcohol

use suggest, however, that the consequences of heavy drinking in adolescence extend beyond those related to a greater risk of injury and accidents, and even beyond increased chances of being diagnosed with alcohol dependence later in life; functional impairment in educational, occupational, social and academic domains extends well into adulthood (Dawes et al, 2000; Parry et al, 2004; Schuckit, 2009; Zeigler et al, 2005). Furthermore, because the brain is not fully mature at adolescence, any neurotoxic insult experienced at this stage can have far-reaching structural and functional consequences (for reviews, see Brown & Tapert, 2004; Monti et al, 2005). Neuroimaging studies suggest that the hippocampus and prefrontal cortex are particularly vulnerable, and that white matter integrity (eg, in the corpus callosum) is negatively affected by heavy drinking during adolescence (eg, De Bellis et al, 2000, 2008; Squeglia et al, 2009; Tapert et al, 2003).

These adverse effects on brain structure lead, predictably, to adverse effects on cognitive functioning. Longitudinal and cross-sectional studies of adolescents with AUD have shown that there are subtle but detectable deficits in general intellectual functioning, psychomotor functioning, processing speed, attention, memory for verbal and nonverbal information, and executive function (Brown & Tapert, 2004; Moss et al, 1994; Tapert et al, 2002; Zeigler et al, 2005).

One major complicating factor in the interpretation of data presented in the studies cited above is that their samples were drawn largely from populations of treatment-seeking adolescents with AUD. As is the case in adults, however, treatment-seeking adolescents represent only a small proportion of the overall AUD population; most AUD adolescents are community-dwelling and treatment-naïve. Furthermore, any attempt to generalise research findings from treatment-seeking samples to the treatment-naïve population would be mistaken: treatment-seeking AUD individuals tend to consume substantially more alcohol, and to be much more likely to present with psychiatric comorbidity and extensive neural damage, than treatment-naïve AUD individuals (Di Sclafani et al, 2008; Fein et al, 2002; Fein & Landman, 2005). Furthermore, many of the samples used in the studies reviewed above featured individuals with polysubstance abuse. This fact makes it difficult to disentangle impairments in cognitive function due to alcohol use from those due to, for instance, cannabis and stimulant use.

To address these methodological issues, and to thereby provide some clarity on the effects of alcohol on adolescent neuropsychological functioning, a team led by George Fein (Neurobehavioral Research, Inc), Susan Tapert (University of California, San Diego), Paul Carey (University of Stellenbosch) and Dan Stein (University of Cape Town), and involving other researchers from the University of Stellenbosch and the University of Cape Town, initiated a research programme examining community-dwelling, treatment-naïve adolescents with AUD in Cape Town (NIH grant RO1 AA016303-01; PI: G. Fein). South African adolescents tend to prefer alcohol as a substance of abuse, and the incidence of polysubstance abuse in Cape Town schools is much lower than that in the United States, where much of the previous research in this field has originated (Flisher et al, 2003; Parry et al, 2004; Plüddemann et al, 2009). Studying adolescent AUD in South Africa therefore provides a relatively unique opportunity to sample from a reasonably pure and untreated population, and hence to make stronger claims to understanding the effects of heavy alcohol use on the adolescent brain.

In the first paper to emerge from that research collaboration, Ferrett et al (2010) reported the comparison of a group of alcohol-dependent adolescents (n = 26) with a control group of adolescents with no, or very little, history of alcohol consumption (n = 26). The groups were matched on all major demographic variables, and all participants were free of other substance use disorders, externalising pathology and psychiatric, medical or neurological disorders. Regression analyses of data from a comprehensive battery of neuropsychological tests revealed that group membership (AUD versus control) contributed to a significant portion of the variance in performance on measures of psychomotor functioning, verbal memory and one aspect of executive functioning (viz, the ability to self-monitor behaviour), even after controlling for tobacco use and demographic characteristics.

These preliminary results suggest that, consistent with data from earlier studies, AUD adolescents do indeed show subtle deficits in discrete cognitive domains. The current data are important, however, because they establish the presence of these deficits even in the absence of polysubstance abuse and psychiatric comorbidity. The observed cognitive deficits might, of course, be larger in samples with such abuse and comorbidity; comparative studies of such South African adolescent populations are forthcoming.

Finally, it is worth noting that almost 40% of the participants in the AUD group in this study smoked cigarettes regularly. Recent research suggests that chronic cigarette smoking in the context of primary AUD has the potential to magnify neurobiological and neuropsychological impairment, and to alter the course of recovery in abstinent individuals (Durazzo & Meyerhoff, 2007). These additive effects of smoking have not yet been studied in an AUD population such as is the focus of the Cape Town collaboration; investigations along those lines might therefore be enlightening.

Conclusion

When clinical neuropsychologists are asked to assess individuals with alcohol-use disorders, they face challenges with regard to heterogeneity: aetiology, forms and location of neural damage, and of functional outcomes. As our review suggests, the existing literature in this field spans an enormous range, but if the clinician is to conduct an effective assessment, and is to deliver insightful treatment recommendations, it is critical that he/she keeps abreast of the latest scientific developments with regard to the heterogeneity, at every level, that characterises AUD. It is also important that the clinician uses appropriate tools. For instance, as we have emphasised, impaired executive function is characteristic of even long-term abstinent alcoholics, but only the use of appropriately specialised assessment instruments will allow the detection of relatively subtle deficits within the broad category of executive abilities.

Our review also makes it clear, we hope, that ongoing research into the neurocognitive effects of alcohol abuse and dependence must involve cross-disciplinary teams and must assume an integrative approach: genetic and family variables must be adequately assessed, demographic variables must be taken into account; structural damage must be accurately measured; and functional changes across multiple domains must be evaluated. The research neuropsychologist is a vital member of this cross-disciplinary team. He/she is best qualified to select and administer a cognitive test battery that will identify patterns and magnitude of

deficit and sparing, allow the quantification of recovery with abstinence, and indicate the best approach to rehabilitation. Furthermore, the well-trained neuropsychologist will be able to integrate findings from structural and functional neuroimaging sessions, electrophysiological measures, genetic tests and neurocognitive test batteries, and will therefore be best placed to assume a position at the heart of an integrative approach to the assessment and treatment of individuals with alcohol use disorders.

References

Adams, K.M. & Grant, I. (1984). Failure of non-linear models of drinking history variables to predict neuropsychological performance in alcoholics. *American Journal of Psychiatry*, 141(5):663–67.

Baddeley, A. & Hitch, G. (1974). Working memory. In G.H. Bower (ed.) *Recent Advances in Learning and Motivation.* New York: Academic Press.

Bates, M.E., Bowden, C. & Barry, D. (2002). Neurocognitive impairment associated with alcohol use disorders: implications for treatment. *Experimental and Clinical Psychopharmacology*, 10(3):193–212.

Bates, M.E., Voelbel, G.T., Buckman, J.F., Labouvie, E.W. & Barry, D. (2005). Short-term neuropsychological recovery in clients with substance abuse disorders. *Alcoholism: Clinical and Experimental Research*, 29(3):367–77.

Beatty, W., Hames, K., Blanco, C., Nixon, S. & Tivis, L. (1996). Visuospatial perception, construction and memory in alcoholism. *Journal of Studies on Alcohol*, 57(2):136–43.

Bechara, A., Dolan, S., Denburg, N., Hindes, A., Anderson, S.W. & Nathan, P.E. (2001). Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia*, 39(4):376–89.

Begleiter, H. & Porjesz, B. (1999). What is inherited in the predisposition toward alcoholism? A proposed model. *Alcoholism: Clinical and Experimental Research*, 23(7):1125–35.

Bigler, E.D. (2009). Hans-Lukas Teuber and 'The Riddle of Frontal Lobe Function in Man' as published in *The Frontal Granular Cortex and Behavior* (1964). *Neuropsychology Review*, 19(1):9–24.

Blume, A.W. & Marlatt, G.A. (2009). The role of executive cognitive functions in changing substance use: what we know and what we need to know. *Annals of Behavioral Medicine*, 37(2):117–25.

Brandt, J., Butters, N., Ryan, C. & Bayog, R. (1983). Cognitive loss and recovery in long-term alcohol users. *Archives of General Psychiatry*, 40(4):435–42.

Brown, S.A. & Tapert, S.F. (2004). Adolescence and the trajectory of alcohol use: basic to clinical studies. *Annals of the New York Academy of Sciences*, 1021:234–44.

Clarke, J. & Haughton, H. (1975). A study of intellectual impairment and recovery rates in heavy drinkers in Ireland. *British Journal of Psychiatry*, 126:178–84.

Dao-Castellana, M.H., Samson, Y., Legault, F., Martinot, J.L., Aubin, H.J., Crouzel, C., Feldman, L., Barracund, D., Rancurel, G., Feline, A. & Syrota, A. (1998). Frontal dysfunction in neurologically normal chronic alcoholic subjects: metabolic and neuropsychological findings. *Psychological Medicine*, 28(5):1039–48.

Dawes, M.A., Antelman, S.M., Vanyukov, M.M., Giancola, P., Tarter, R.E., Susman, E.J., Mezzich, A. & Clark, D.B. (2000). Developmental sources of variation in liability to adolescent substance use disorders. *Drug and Alcohol Dependence*, 61(1): 3–14.

De Bellis, M.D., Clark, D.B., Beers, S.R., Soloff, P.H., Boring, A.M., Hall, J., Kersh, A. & Keshavan, M.S. (2000). Hippocampal volume in adolescent-onset alcohol use disorders. *American Journal of Psychiatry*, 157(5):737–44.

De Bellis, M.D., Van Voorhees, E., Hooper, S.R., Gibler, N., Nelson, L., Hege, S.G., Payne, M.E. & MacFall, J. (2008). Diffusion tensor measures of the corpus callosum in adolescents with adolescent onset alcohol use disorders. *Alcoholism: Clinical and Experimental Research*, 32(3):395–404.

Di Sclafani, V., Ezekiel, F., Meyerhoff, D.J., Mackay, S., Dillon, W.P., Weiner, M.W. & Fein, G. (1995). Brain atrophy and cognitive function in older abstinent alcoholic men. *Alcoholism: Clinical and Experimental Research*, 19(5):1121–26.

Di Sclafani, V., Finn, P. & Fein, G. (2008) Treatment-naive active alcoholics have greater psychiatric comorbidity than normal controls but less than treated abstinent alcoholics. *Drug and Alcohol Dependence*, 98(1):115–22.

Dick, D.M. & Foroud, T. (2003). Candidate genes for alcohol dependence: a review of genetic evidence from human studies. *Alcoholism: Clinical and Experimental Research*, 27(5):868–79.

Dubois, B., Slachevsky, A., Litvan, I. & Pillon, B. (2000). The FAB: a frontal assessment battery at bedside. *Neurology*, 55(11):1621–26.

Duff, K., Patton, D., Schoenberg, M.R., Mold, J., Scott, J.G. & Adams, R.L. (2003). Age- and education-corrected independent normative data for the RBANS in a community dwelling elderly sample. *Clinical Neuropsychologist*, 17(3):351–66.

Dufour, M.C. & Fuller, R.K. (1995). Alcohol in the elderly. *Annual Review of Medicine*, 46:123–32.

Durazzo, T.C. & Meyerhoff, D.J. (2007). Neurobiological and neurocognitive effects of chronic cigarette smoking and alcoholism. *Frontiers in Bioscience*, 12:4079–100.

Edenberg, H.J. & Foroud, T. (2006). The genetics of alcoholism: Identifying specific genes through family studies. *Addiction Biology*, 11(3–4):386–96.

Fama, R., Pfefferbaum, A. & Sullivan, E.V. (2004). Perceptual learning in detoxified alcoholic men: contributions from explicit memory, executive function, and age. *Alcoholism: Clinical and Experimental Research*, 28(11):1657–65.

Fein, G., Bachman, L., Fisher, S. & Davenport, L. (1990). Cognitive impairments in abstinent alcoholics. *The Western Journal of Medicine*, 152(5):531–37.

Fein, G., Di Sclafani, V., Cardenas, V.A., Goldmann, H., Tolou-Shams, M. & Meyerhoff, D.J. (2002). Cortical gray matter loss in treatment-naive alcohol dependent individuals. *Alcoholism: Clinical and Experimental Research*, 26(4):558–64.

Fein, G. & Landman, B. (2005). Treated and treatment-naive alcoholics come from different populations. *Alcohol*, 35(1):19–26.

Fein, G. & McGillivray, S. (2007). Cognitive performance in long-term abstinent elderly alcoholics. *Alcoholism: Clinical and Experimental Research*, 31(11):1788–99.

Ferrett, H.L., Carey, P.D., Thomas, K.G.F., Tapert, S.F. & Fein, G. (2010). Neuropsychological performance of South African treatment-naive adolescents with alcohol dependence. *Drug and Alcohol Dependence*, 110(1–2):8–14.

Finn, P.R., Rickert, M.E., Miller, M.A., Lucas, J., Bogg, T., Bobova, L. & Cantrell, H. (2009). Reduced cognitive ability in alcohol dependence: examining the role of covarying externalizing psychopathology. *Journal of Abnormal Psychology*, 118(1):100–116.

Finn, P.R., Sharkansky, E.J., Brandt, K.M. & Turcotte, N. (2000). The effects of familial risk, personality, and expectancies on alcohol use and abuse. *Journal of Abnormal Psychology*, 109(1):122–33.

Flannery, B., Fishbein, D., Krupitsky, E., Langevin, D., Verbitskaya, E., Bland, C., Bolla, K., Egorova, V., Bushara, N., Tsoy, M. & Zvartau, E. (2007). Gender differences in neurocognitive functioning among alcohol-dependent Russian patients. *Alcoholism: Clinical and Experimental Research*, 31(5):745–54.

Flisher, A.J., Parry, C.D.H., Evans, J., Muller, M. & Lombard, C. (2003). Substance use by adolescents in Cape Town: prevalence and correlates. *The Journal of Adolescent Health*, 32(1):58–65.

Glenn, S.W. & Parsons, O.A. (1991). Impaired efficiency in female alcoholics' neuropsychological performance. *Journal of Clinical and Experimental Neuropsychology*, 13(6):895–908.

Glenn, S.W. & Parsons, O.A. (1992). Neuropsychological efficiency measures in male and female alcoholics. *Journal of Studies on Alcohol*, 53(6):546–52.

Godding, P.R., Fitterling, J.M., Schmitz, J.M., Seville, J.L. & Parisi, S.A. (1992). Discriminative utility of a brief cognitive status assessment with alcoholics and the impact of cognitive status on acquisition of treatment-relevant information. *Psychology of Addictive Behaviors*, 6(1):34–40.

Goldstein, R.Z. & Volkow, N.D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*, 159(10):1642–52.

Gontovsky, S.T., Beatty, W.W. & Mold, J.W. (2004). Repeatable Battery for the Assessment of Neuropsychological Status in a normal, geriatric sample. *Clinical Gerontologist*, 27(3):79–86.

Grant, B.F., Stinson, F.S., Dawson, D.A., Chou, S.P., Dufour, M.C., Compton, W., Pickering, R.P. & Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. Results from the national epidemiological survey on alcohol and related conditions. *Archives of General Psychiatry*, 61: 807–16.

Grant, I. (1987). Alcohol and the brain: neuropsychological correlates. *Journal of Consulting and Clinical Psychology*, 55(3):310–24.

Green, A., Garrick, T., Sheedy, D., Blake, H., Shores, E. & Harper, C. (2010). The effect of moderate to heavy alcohol consumption on neuropsychological performance as measured by the Repeatable Battery for the Assessment of Neuropsychological Status. *Alcoholism: Clinical and Experimental Research*, 34(3):443–50.

Harper, C.G. (1998). The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? *Journal of Neuropathology and Experimental Neurology*, 57(2): 101–10.

Harper, C.G., Kril, J.J. & Holloway, R.L. (1985). Brain shrinkage in chronic alcoholics: a pathological study. *British Medical Journal*, 209(6467):501–504.

Harper, C.G. & Matsuomoto, I. (2005). Ethanol and brain damage. *Current Opinion in Pharmacology*, 5(1):73–78.

Harris, G.J., Jaffin, S.K., Hodge, S.M., Kennedy, D., Caviness, V.S., Marinkovic, K., Papadimitriou, G.M., Makris, N. & Oscar-Berman, M. (2008). Frontal white matter and cingulum diffusion tensor imaging deficits in alcoholism. *Alcoholism: Clinical and Experimental Research*, 32(6):1001–13.

Hook, J.N., Han, D.Y. & Smith, C.A. (2010). Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and depressive complaints in older adults. *Clinical Gerontologist*, 33(2):84–91.

Ihara, H., Berrios, G.E. & London, M. (2000). Group and case study of the dysexecutive syndrome in alcoholism without amnesia. *Journal of Neurology, Neurosurgery and Psychiatry*, 68(6):731–37.

Johnson-Greene, D., Adams, K.M., Oilman, S., Koeppe, R.A., Junck, L., Kluin, K.J., Martorello, S. & Heumann, M. (1997). Effects of abstinence and relapse upon neuropsychological function and cerebral glucose metabolism in severe chronic alcoholism. *Journal of Clinical and Experimental Neuropsychology*, 19(3):378–85.

Jurado, M.B. & Rosselli, M. (2007). The elusive nature of executive functions: a review of our current understanding. *Neuropsychology Review*, 17(3):213–33.

Larson, E.B., Kirschner, K., Bode, R., Heinemann, A. & Goodman, R. (2005). Construct and predictive validity of the Repeatable Battery for the Assessment of Neuropsychological Status in the evaluation of stroke patients. *Journal of Clinical and Experimental Neuropsychology*, 27(1):16–32.

Lezak, M.D., Howieson, D.B. & Loring, D.W. (eds) (2004). *Neuropsychological Assessment*. 4th edition. New York: Oxford University Press.

Lim, M.-L., Collinson, S.L., Feng, L. & Ng, T.-P. (2010). Cross-cultural application of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): performances of elderly Chinese Singaporeans. *Clinical Neuropsychologist*, 24(5):811–26.

Liu, I.-C., Chiu, C.-H. & Yang, T.-T. (2010). The effects of gender and a co-occurring depressive disorder on neurocognitive functioning in patients with alcohol dependence. *Alcohol and Alcoholism*, 45(3):231–36.

Makris, N., Oscar-Berman, M., Kim, S., Hodge, S.M., Kennedy, D.N., Caviness, V. S., Marinkovic, K., Breiter, H.C., Gasic, G.P. & Harris, G.J. (2008). Decreased volume of the brain reward system in alcoholism. *Biological Psychiatry*, 64(3):192–202.

Mann, K., Gunther, A., Stetter, F. & Ackermann, K. (1999). Rapid recovery from cognitive deficits in abstinent alcoholics: a controlled test-retest study. *Alcohol and Alcoholism*, 34(4):567–74.

May, P., Gossage, J., Marais, A., Adnams, C., Hoyme, H., Jones, K., Robinson, L., Khaole, N., Snell, C., Kalberg, W., Hendricks, L., Brooke, L., Stellavato, C. & Viljoen, D. (2007). The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. *Drug and Alcohol Dependence*, 88(2–3):259–71.

Mazas, C.A., Finn, P.R. & Steinmetz, J.E. (2000). Decision-making biases, antisocial personality, and early-onset alcoholism. *Alcoholism: Clinical and Experimental Research*, 24(7):1036–40.

Medina, K.L., Shear, P.K., Schafer, J., Armstrong, T.G. & Dyer, P. (2004). Cognitive functioning and length of abstinence in polysubstance dependent men. *Archives of Clinical Neuropsychology*, 19(2):245–58.

Mega, M.S. & Cummings, J.L. (1994). Frontal-subcortical circuits and neuropsychiatric disorders. *Journal of Neuropsychiatry and Clinical Neurosciences*, 6(4):358–70.

Meier, P. & Seitz, H.K. (2008). Age, alcohol metabolism and liver disease. *Current Opinion in Clinical Nutrition & Metabolic Care*, 11(1):21–26.

Miller, L. (1991). Predicting relapse and recovery in alcoholism and addiction: neuropsychology, personality, and cognitive style. *Journal of Substance Abuse Treatment*, 8(4):277–91.

Monti, P. M., Miranda, R., Jr., Nixon, K., Sher, K.J., Swartzwelder, H.S., Tapert, S.F., White, A. & Crews, F.T. (2005). Adolescence: booze, brains, and behavior. *Alcoholism: Clinical and Experimental Research*, 29(2):207–20.

Moriyama, Y., Mimura, M., Kato, M., Yoshino, A., Hara, T., Kashima, H., Kato, A. & Watanabe, A. (2002). Executive dysfunction and clinical outcome in chronic alcoholics. *Alcoholism: Clinical and Experimental Research*, 26(8):1239–44.

Moselhy, H.F., Georgiou, G. & Kahn, A. (2001). Frontal lobe changes in alcoholism: a review of the literature. *Alcohol and Alcoholism*, 36(5):357–68.

Moss, H.B., Kirisci, L., Gordon, H.W. & Tarter, R.E. (1994). A neuropsychologic profile of adolescent alcoholics. *Alcoholism: Clinical and Experimental Research*, 18(1):159–63.

Munro, C.A., Saxton, J. & Butters, M.A. (2000). The neuropsychological consequences of abstinence among older alcoholics: a cross-sectional study. *Alcoholism: Clinical and Experimental Research*, 24(10):1510–16.

Nell, V. (2000). *Cross-cultural Neuropsychological Assessment: Theory and Practice*. Mahwah, NJ: Lawrence Erlbaum.

Nixon, S.J. & Parsons, O.A. (1991). Alcohol-related efficiency deficits using an ecologically valid test. *Alcoholism: Clinical and Experimental Research*, 15(4):601–606.

Nixon, S.J., Tivis, R. & Parsons, O.A. (1995). Behavioral dysfunction and cognitive efficiency in male and female alcoholics. *Alcoholism: Clinical and Experimental Research*, 19(3):577–81.

Noel, X., Van der Linden, M., Schmidt, N., Sferrazza, R., Hanak, C., Le Bon, O., De Mol, J., Kornreich, C., Pelc, I. & Verbanck, P. (2001). Supervisory attentional system in nonamnesic alcoholic men. *Archives of General Psychiatry*, 58(12):1152–58.

O'Neill, J., Cardenas, V.A. & Meyerhoff, D.J. (2001). Effects of abstinence on the brain: quantitative magnetic resonance imaging and magnetic resonance spectroscopic imaging in chronic alcohol abuse. *Alcoholism: Clinical and Experimental Research*, 25(11):1673–82.

Oscar-Berman, M. & Marinkovic, K. (2003). Alcoholism and the brain: an overview. *Alcohol Research and Health*, 27(2):125–33.

Oscar-Berman, M. & Marinkovic, K. (2007). Alcohol: effects on neurobehavioral functions and the brain. *Neuropsychology Review*, 17(3):239–57.

Parry, C.D.H., Myers, B., Morojele, N.K., Flisher, A.J., Bhana, A., Donson, H. & Plüddemann, A. (2004). Trends in adolescent alcohol and other drug use: findings from three sentinel sites in South Africa (1997–2001). *Journal of Adolescence*, 27(4):429–40.

Parry, C.D.H., Plüddemann, A., Steyn, K., Bradshaw, D., Norman, R. & Laubscher, R. (2005). Alcohol use in South Africa: findings from the first Demographic and Health Survey (1998). *Journal of Studies on Alcohol*, 66(1):91–97.

Parsons, O.A. (1983). Cognitive dysfunction and recovery in alcoholics. *Substance and Alcohol Actions/Misuse*, 4(2–3):175–90.

Parsons, O.A., Butters, N. & Nathan, P.E. (eds) (1987). *Neuropsychology of Alcoholism: Implications for Diagnosis and Treatment*. New York: Guilford.

Patton, D.E., Duff, K., Schoenberg, M.R., Mold, J., Scott, J.G. & Adams, R.L. (2003). Performance of cognitively normal African Americans on the RBANS in community dwelling older adults. *Clinical Neuropsychologist*, 17(4):515–30.

Petrakis, I.L., Gonzalez, G., Rosenheck, R. & Krystal, J.H. (2002). Comorbidity of alcoholism and psychiatric disorders. *Alcohol Research and Health*, 26(1):81–89.

Pfefferbaum, A., Adalsteinsson, E. & Sullivan, E.V. (2006). Dysmorphology and microstructural degradation of the corpus callosum: interaction of age and alcoholism. *Neurobiology of Aging*, 27(7):994–1009.

Pfefferbaum, A., Sullivan, E.V., Mathalon, D.H. & Lim, K.O. (1997). Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcoholism: Clinical and Experimental Research*, 21(3):521–29.

Pitel, A.L., Beaunieux, H., Witkowski, T., Vabret, F., Guillery-Girard, B., Quinette, P., Desgranges, B. & Eustache, F. (2007). Genuine episodic memory deficits and executive dysfunctions in alcoholic subjects early in abstinence. *Alcoholism: Clinical and Experimental Research*, 31(7):1169–78.

Plüddemann, A., Dada, S., Parry, C., Bhana, A., Perreira, T., Carelsen, A., Kitleli, N., Gerber, W., Rosslee, C. & Fourie, D. (2009). *SACENDU Research Brief Vol. 12(1): Monitoring Alcohol and Drug Abuse Trends in South Africa (July 1996–December 2008)*. Cape Town: Medical Research Council.

Pozzato, G., Moretti, M., Franzin, F., Croce, L.S., Lacchin, T., Benedetti, G., Sablich, R., Stebel, M. & Campanacci, L. (1995). Ethanol-metabolism and aging – the role of first-pass-metabolism and gastric alcohol-dehydrogenase activity. *Journals of Gerontology Series A–Biological Sciences and Medical Sciences*, 50(3):B135–B141.

Randolph, C., Tierney, C.M., Mohr, E. & Chase, N.T. (1998). Repeatable Battery for the Assessment of Neuropsychological Status as a screening test (RBANS): preliminary clinical validity. *Journal of Clinical and Experimental Neuropsychology*, 20(3):310–19.

Ratti, M.T., Bo, P., Giardini, A. & Soragna, D. (2002). Chronic alcoholism and the frontal lobe: which executive functions are impaired? *Acta Neurologica Scandinavica*, 105(4):276–81.

Reed, R.J., Grant, I. & Rourke, S.B. (1992). Long-term abstinent alcoholics have normal memory. *Alcoholism: Clinical and Experimental Research*, 16(4):677–83.

Rourke, S.B. & Grant, I. (1999). The interactive effects of age and length of abstinence on the recovery of neuropsychological functioning in chronic male alcoholics: A 2-year follow-up study. *Journal of the International Neuropsychological Society*, 5(3):234–46.

Rourke, S.B. & Loberg, T. (1996). The neurobehavioral correlates of alcoholism. In I. Grant & K.M. Adams (eds). *Neuropsychological Assessment of Neuropsychiatric Disorders*. New York: Oxford University Press.

Schuckit, M. (2009). Alcohol-use disorders. *Lancet*, 373(9662):492–501.

Schulte, T., Sullivan, E.V., Muller-Oehring, E.M., Adalsteinsson, E. & Pfefferbaum, A. (2005). Corpus callosal microstructural integrity influences interhemispheric processing: a diffusion tensor imaging study. *Cerebral Cortex*, 15(9):1384–92.

Shuttleworth-Jordan, A.B. (1996). On not reinventing the wheel: a clinical perspective on culturally relevant test usage in South Africa. *South African Journal of Psychology*, 26(2):96–102.

Skinner, F.K., MacDonell, L.E.F., Glen, E.M.T. & Glen, A.I.M. (1989). Repeated automated assessment of abstinent male alcoholics: essential fatty acid supplementation and age effects. *Alcohol and Alcoholism*, 24(2):129–39.

Smith, D.E. & McCrady, B.S. (1991). Cognitive impairment among alcoholics: impact on drink refusal skill acquisition and treatment outcome. *Addictive Behaviors*, 16(5):265–74.

Solomon, D.A. & Malloy, P.F. (1992). Alcohol, head injury, and neuropsychological function. *Neuropsychology Review*, 3(3):249–80.

Spencer, R.L. & Hutchinson, K.E. (1999). Alcohol, aging, and the stress response. *Alcohol Research & Health*, 23(4):272–83.

Squeglia, L.M., Jacobus, J. & Tapert, S.F. (2009). The influence of substance use on adolescent brain development. *Clinical EEG and Neuroscience*, 40(1):31–38.

Stuss, D.T. & Levine, B. (2002). Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annual Review of Psychology*, 53:401–33.

Sullivan, E.V. (2007). Alcohol and drug dependence: brain mechanisms and behavioral impact. *Neuropsychology Review*, 17(3):235–38.

Sullivan, E.V., Deshmukh, A., Desmond, J.E., Lim, K.O. & Pfefferbaum, A. (2000). Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: relation to ataxia. *Neuropsychology*, 14(3):341–52.

Sullivan, E.V., Fama, R., Rosenbloom, M.J. & Pfefferbaum, A. (2002). A profile of neuropsychological deficits in alcoholic women. *Neuropsychology*, 16(1):74–83.

Sullivan, E.V., Rosenbloom, M.J. & Pfefferbaum, A. (2000b). Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcoholism: Clinical and Experimental Research*, 24(5):611–21.

Tapert, S.F., Cheung, E.H., Brown, G.G., Frank, L.R., Paulus, M.P., Schweinsburg, A.D., Meloy, M.J. & Brown, S.A. (2003). Neural response to alcohol stimuli in adolescents with alcohol use disorder. *Archives of General Psychiatry*, 60(7):727–35.

Tapert, S.F., Granholm, E., Leedy, N.G. & Brown, S.A. (2002). Substance use and withdrawal: neuropsychological functioning over 8 years in youth. *Journal of the International Neuropsychological Society*, 8(7):873–83.

Tapert, S.F., Pulido, C., Paulus, M.P., Schuckit, M.A. & Burke, C. (2004). Level of response to alcohol and brain response during visual working memory. *Journal of Studies on Alcohol*, 65(6):692–700.

Tapert, S.F., Schweinsburg, A.D., Barlett, V.C., Brown, S.A., Frank, L.R., Brown, G.G. & Meloy, M.J. (2004). Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. *Alcoholism: Clinical and Experimental Research*, 28(10):1577–86.

Teichner, G., Horner, M.D. & Harvey, R.T. (2001). Neuropsychological predictors of the attainment of treatment objectives in substance abuse patients. *International Journal of Neuroscience*, 106(3–4):253–63.

Teuber, H.-L. (1964). The riddle of frontal lobe function in man. In J. Warren & K. Akert (eds). *The Frontal Granular Cortex and Behavior.* New York: McGraw-Hill.

Tuck, R.R. & Jackson, M. (1991). Social, neurological and cognitive disorders in alcoholics. *Medical Journal of Australia*, 155(4):225–29.

Urban, M., Chersich, M.F., Fourie, L.A., Chetty, C., Olivier, L. & Viljoen, D. (2008). Fetal Alcohol Syndrome among Grade 1 schoolchildren in Northern Cape Province: prevalence and risk factors. *South African Medical Journal*, 98(11):877–82.

Vollstadt-Klein, S., Hermann, D., Rabinstein, J., Wichert, S., Klein, O., Ende, G. & Mann, K. (2010). Increased activation of the ACC during a spatial working memory task in alcohol-dependence versus heavy social drinking. *Alcoholism: Clinical and Experimental Research*, 34(5):771–76.

Wilk, C.M., Gold, J.M., Bartko, J.J., Dickerson, F., Fenton, W.S., Knable, M., Randolph, C. & Buchanan, R.W. (2002). Test-retest stability of the Repeatable Battery for the Assessment of Neuropsychological Status in schizophrenia. *American Journal of Psychiatry*, 159(5):838–44.

Yonker, J.E., Nilsson, L.G., Herlitz, A. & Anthenelli, R.M. (2005). Sex differences in spatial visualization and episodic memory as a function of alcohol consumption. *Alcohol and Alcoholism*, 40(3):201–207.

Zago-Gomes, M.D. & Nakamura-Palacios, E.M. (2009). Cognitive components of frontal lobe function in alcoholics classified according to Lesch's typology. *Alcohol and Alcoholism*, 44(5):449–57.

Zeigler, D.W., Wang, C.C., Yoast, R.A., Dickinson, B.D., McCaffree, M.A., Robinowitz, C.B. & Sterling, M.L. (2005). The neurocognitive effects of alcohol on adolescents and college students. *Preventive Medicine*, 40(1):23–32.

Zinn, S., Stein, R. & Swartzwelder, H.S. (2004). Executive functioning early in abstinence from alcohol. *Alcoholism: Clinical and Experimental Research*, 28(9):1338–46.

Zipursky, R.B., Lim, K.O. & Pfefferbaum, A. (1989). MRI study of brain changes with short-term abstinence from alcohol. *Alcoholism: Clinical and Experimental Research*, 13(5):664–67.

10 Neuropsychoanalytic notes on addiction

Mark Solms, Eleni Pantelis and Jaak Panksepp

Introduction

Freud had remarkably little to say about addiction, save for this one observation, made early in his psychological work (and often repeated thereafter):

> It has dawned on me that masturbation is the one major habit, the 'primal addiction' and that it is only as a substitute and replacement for it that the other addictions – for alcohol, morphine, tobacco, etc., – come into existence. (Freud, 1897:272)

A minor elaboration of this view is the following one, also made early in Freud's work:

> Not everyone who has occasion to take morphia, cocaine, chloral-hydrate, and so on, for a period, acquires in this way an 'addiction' to them. Closer enquiry usually shows that these narcotics are meant to serve – directly or indirectly – as a substitute for a lack of sexual satisfaction.' (Freud 1898:276)

In other words, during development masturbation is normally replaced by adult sexual satisfaction, but where it is not it may be substituted by (another) addiction.

These are quintessentially Freudian claims, museum-quality examples of the type. For that reason, perhaps, they are all too easily dismissed by addiction researchers today. If readers are willing to suspend judgment for a moment, though, and permit us to unpack the meaning of these claims and reconsider them in the light of contemporary neuroscience, their patience will be amply repaid.

For all of his failings, Freud had an uncanny ability to identify the essence of a psychological problem. The fundamental problem of addiction exposed by the parallel that Freud drew with masturbation is that substance abuse (like masturbation) is an affectively rewarding activity that serves no biological purpose. Substance abuse generates hedonically positive affects in the brain (or reduces negative ones; for full discussion of this 'opponent process' issue in addiction research, see Khantzian, 2003) but does not sustain reproductive fitness. In fact, it does the opposite. Addiction therefore cannot be an evolutionarily proper use of the brain mechanisms in question, but it is psychologically compelling nonetheless.

Substance abuse vs masturbation

Substance abuse appears to employ brain mechanisms that were evolutionarily designed to reward biologically useful activities (like copulation, as opposed to masturbation) (see also

Chapter 5). This is what pleasurable affects are *for*, evolutionarily speaking; they reward biologically useful actions, and thus motivate animals to perform the work that is necessary to achieve them (Solms & Nersessian, 1999; Damasio 1999). The word 'abuse' in 'substance abuse' refers to the fact that the pleasure is attained without the natural effort and persistence it was designed to reward. The motivation to perform the effortful work to achieve biologically useful goals in an indifferent and even hostile world is substituted by mere self-administration of pleasure-producing (or unpleasure-reducing) substances. This requires hardly any effort at all, aside from acquiring drugs that are not legally available, and nothing biologically useful is achieved by it. Part of the affective prize is thus attained without actually taking part in the social pursuit and competition for gratification. The biological purpose of reward is cheated. A cheap form of affect has been traded for reproductive fitness.

Herein presumably lies the root of our moral condemnation of both masturbation and addiction alike.

This conclusion seems to be the implication of the second Freud quotation above: substance abuse (like masturbation) is an inferior *substitute* for 'real' sources of satisfaction (like copulation). Substance abuse, like masturbation, represents a failure to negotiate the transition from infantile self-soothing to mastery of the real external world – the arena of all the competitions that we simply have to enter in order to survive and reproduce.

This begs the question: why and how do we normally negotiate this transition? What enables us to give up effortless masturbatory/addictive pleasures in favour of real ones, in favour of the biologically (and morally) wholesome ones? If we can trace the mechanism by which we normally traverse this transition, we will have identified the pivotal locus of the biological failure (of the psychopathology) called addiction.

It seems unlikely that evolution would have left this important task to moral persuasion (education or learning) alone. There must be some intrinsic mechanism that motivates us to forego empty pleasures in favour of the more difficult and risky business of engagement with the real world. And there does appear to be just such an intrinsic mechanism, the identification of which reveals important shortcomings in many contemporary conceptualisations of the neural basis of reward.

If the biology of reward entailed a unitary brain mechanism, such as the one that many eminent researchers still seem to claim for the mesocortical-mesolimbic dopamine (DA) 'reward system' (Haber & Knutson, 2009; Rolls, 1999), then it is difficult to imagine why animals would ever bother to negotiate the task just mentioned. Why not just go straight for the reward, and bypass the effort and risk involved in the activities that 'properly' generate them? It comes as no surprise to us to learn, therefore, that the mammalian brain does contain a more complex reward mechanism which drives us to seek our pleasures in the external world. This latter mechanism is indeed the mesocortical-mesolimbic DA system, but it turns out to not be a simple 'reward' system at all – despite the fact that *almost all drugs of abuse* (like all forms of appetitive behaviour) *do indeed massively increase DA activity in this system*.

Seeking reward

The mistaken attribution of simple reward functions to the mesocortical-mesolimbic DA system was first appreciated by Panksepp (1982, 1986). He observed that artificial

stimulation of this (D2-receptor-mediated) motivational DA system does not generate pleasurable feelings and blissful satiation in mammals, as *consummation* of a need normally should. Rather it impels the animal to excitedly *seek more of the stimulation* (in other words, it actually increases the *appetitive* drive that *leads* us to rewards, rather than the consummation behaviour that actually *delivers* them). This and subsequent research led Panksepp to rename the DA 'reward' system a 'SEEKING' system (Panksepp 1998; capitals in the original). The SEEKING system motivates animals to engage with the world – to eagerly forage, to curiously explore, to optimistically expect – in short, *to look to the outside world for attaining pleasurable experiences*. The SEEKING system is stimulated into action internally by medial hypothalamic 'need detector' mechanisms, and externally by enticing opportunities in the world. And when it is activated it impels the animal to engage with the real objects that satisfy its inner needs. This *in turn* generates pleasurable experiences via PLEASURE-LUST (and other) systems, which utilise the SEEKING system for their hedonic ends but which are not themselves mediated by DA alone. These systems will be discussed below.

Berridge and Robinson (1998) were driven to very similar conclusions by their own research findings, which eventually led Berridge (2007) to draw an analogous (but as we shall see, not identical) distinction between the brain mechanisms for 'wanting' and 'liking' in mammals, with 'wanting' being just one step removed from SEEKING. (A full history of the diversity of views in this theoretical hornet's nest is summarized in Alcaro et al, 2007, and Panksepp & Moskal, 2008.)

It is not difficult to see, in light of our reflections on Freud's observations, why an instinctual SEEKING or 'wanting' mechanism would have evolved alongside the PLEASURE or 'liking' mechanism. It is a sad but incontrovertible fact that all our needs cannot be met narcissistically, by mere *feeling* of reward versus *actual achievement* of reward. Biological needs represent a true *lack* in the organism that can only be rectified by an object (and usually a rather specific object) in the outside world. This is one of the great facts of life, and an ultimate source of all its struggles.

The distinction between the brain's appetitive and consummatory 'reward' mechanisms helps to make sense of the fact that addicts do not generally find their substance-induced DA surges to be pleasurable; at times they do not even *like* the objects of their addictive *wants* (Kassel, 2010).

Most recent addiction research into the 'wanting' aspect of the brain's so-called reward mechanisms has, however, not been interpreted within Panksepp's framework as summarised above. It has been interpreted on the view that 'wanting' is equivalent to something quite different from simple SEEKING, something called 'incentive salience' (Robinson & Berridge, 2003). On this view, DA activity is said to *predict* which objects are likely to produce pleasurable experiences (incentive), and thereby to motivate the animal to selectively attend to such objects (salience). Addiction researchers who follow this view (eg, Volkow et al, 2009) accordingly argue that drug-induced DA surges make addicts over-incentivise the drugs that generate such surges – and associated environmental cues – to consider them excessively important (inappropriately salient).

A moment's thought, however, reveals a significant conflation in this view. Drug-induced surges in salience attribution should incentivise the addict to pay extra attention to the *pleasure-generating* things they come across while high, not to the thing (the DA agonist)

that merely induced the high. On Berridge's own theory, the DA agonist is not intrinsically affect-generating. The foraging behaviours (and the associated curious, interested, expectant, optimistic feelings) that DA actually induce, merely increase the chances of the animal encountering the real objects of their needs – the objects that they 'like'. This, a second stage that can only follow the primary 'SEEKING/wanting' process, is what is actually rewarding.

The incentive salience mechanism that Berridge and others attribute to the mesocortical-mesolimbic DA system seems to be a higher-order process in the complex cascade of appetitive eagerness. Firstly, the animal has to (1) be driven to seek the objects of its biological needs in the outside world, surely an invigorating hedonic activity, before it can (2) experience the pleasurable rewards that such objects generate, which in turn enables the animal to (3) learn from such experiences – ie, associate specific objects with the pleasurable relief of each need. Only then can the animal have any basis for predicting biologically appropriate pleasures from the sight or smell of specific objects (ie, attribute incentive salience). In short, incentive-salience has to rely on past learning, while SEEKING is an intrinsic emotional-affective system that allows learning to occur.

Panksepp has always emphasised the intrinsically 'objectless' quality of the SEEKING instinct, calling it 'a goad without a goal' (Panksepp, 1971). Learning comes later, and involves much more than instinct. Learning is a by-product of the encounter between instinct and environment. Learning would never occur if it were not for the existence of a primary instinct toward engagement with the environment – with all the effort, frustration and risk that this entails.

Incentive salience – a learning-based mechanism – therefore reveals itself to be (in Freudian terms) an 'ego' rather than an 'id' mechanism. Ironically, this is also where moral persuasion (the 'superego') may enter the equation. It is no accident that recent research on the role of incentive salience in addiction has strongly emphasised the contribution in addictive pathogenesis of aberrant *inhibitory controls* on the underlying mescortical-mesolimbic DA activity (Baler & Volkow, 2006). All the influences exerted by parents, upbringing, education and the like have their effects on these higher ('learning') aspects of the transition from self-soothing to object mastery. We should therefore be on our guard against overly reductionist attempts to elucidate the basic molecular mechanisms of incentive salience conditioning (Chen, Chen & Chiang 2009) as if it were the same as the primary-process motivation employed in SEEKING resources. The variability contributed to any psychopathology by higher-order environmental factors such as parenting, upbringing and education, as Freud taught us, can be very complicated indeed.

It is to the first two steps in the three-step process outlined above that we must return, then, if we wish to elucidate the hard-wired, instinctual ('id') mechanisms leading from self-soothing to object mastery. There are very special hedonic feeling components to the instinctual systems that support those aspects of survival which require a confrontation with the real world.

We have said already that the first step in the process must be a basic SEEKING tendency, which drives the animal to 'forage' in the outside world, triggered by its detection of an inner need. Why, then, is this simple and primary DA-activated process so heavily implicated in addiction? After all, SEEKING is the step in the putative process that leads the animal *away*

from narcissistic self-soothing (from Freud's 'masturbation'). Why then do substances of abuse *increase* activation of this DA mechanism? Does this not reveal a contradiction in the parallel that Freud drew between masturbation and addiction (which he saw as a fixation upon or regression to self-soothing)?

It certainly would be a contradiction if it were not for the important finding (made in relation to cocaine addiction in the 1980s, and in subsequent studies in relation to methamphetamine, alcohol and heroin, too) that D2 receptors are consistently *decreased* in addicts, even long after the resolution of acute withdrawal effects (Volkow et al, 1990, 1993, 2004). Recent research has also shown that relatively decreased D2 receptors *precede* the development of an addiction – that it may in fact be an important biological marker of addictive vulnerability (Nader et al, 2006; Volkow et al, 2006, 2007). From an affective point of view, this condition would be the opponent-process of the appetitive-SEEKING reward that temporary (ie, artificial pharmacological) arousal of dopamine systems promotes (Johnson, 2008; Khantzian, 2003; Koob & LeMoal, 2001).

These findings are currently being interpreted to mean that individuals with blunted capacity to attribute 'incentive salience' gradually come to learn that only substances that can produce massive surges of D2-mediated activity are salient. But in light of our differences with salience attribution theory in this context, especially at a primary-process level, a better interpretation might be that individuals with blunted SEEKING capacities come to learn (especially if not otherwise helped by parents, educators and the like) that substances which produce massive surges of D2-mediated activity enable them to *gain access to pleasurable experiences and objects in the outside world* that would otherwise be relatively inaccessible to them. The object of the addiction would then not just be the stimulant substance itself – as incentive salience theory suggests – but rather the possibility (or expectation, or even hope) of gaining social, sexual and other biologically useful rewards that the substance artificially evokes. This alternative explanation of the link between reduced D2 receptivity and addiction has important clinical implications, and we believe it deserves careful consideration in future research.

For now, however, coming full circle, it appears that the main focus of the addiction process must still fall back, to a substantial degree, on the pleasurable aspects of rewards. This, and not just the primary SEEKING instinct or the drugs that stimulate it (or the paraphernalia associated with those drugs), seems to remain the ultimate psychological object of addiction, at least at the higher levels of the mental apparatus. Thus, pleasure (or its habituation, and hence relief from the ensuing pain) must remain big-ticket items in addiction research.

Pleasure and opioids

As we have already noted, the PLEASURE-LUST, or 'liking', aspect of the reward process is not just DA-mediated (although DA has a role to play in it). It is generally accepted on current knowledge that the main aspect of the PLEASURE process is mediated by opioids (acting on mu and delta receptors in the basal forebrain region in particular; see Panksepp, 1998; Berridge, 1996). These are very ancient brain molecules, which are thought to have evolved in the brain initially for their *hedonic* properties, but they also served endogenous

analgesic functions and therefore came later to ameliorate the behaviourally more complex *pain of social loss* (Panksepp, 1998). This latter instinctual mechanism – which Panksepp calls the PANIC-GRIEF system – is especially highly developed in mammals, which are exquisitely social animals (but it must have evolved earlier, as it is also present in birds). This system has its epicentre in a neuronal network that courses between anterior cingulate gyrus, various dinecephalic nuclei and the dorsal periaqueductal grey.

The hedonic, analgesic and social-soothing properties of opioids are difficult to separate entirely, especially when considered from the lived viewpoint of what a substance abuser is trying to achieve. A diagnostic differentiation of this kind would certainly be clinically important, as indeed is the more basic distinction we have already drawn between those who are seeking DA stimulation and those who are seeking opioid-mediated euphoria or relief (cf. 'uppers' versus 'downers'). But now we must finally consider the opioid systems as a whole in relation to the Freudian formulation of addiction that we are considering here.

It is easy to see the link between an opiate-induced hedonic fog and the narcissistic delights of masturbation. We have likewise already provided an answer to the question as to why animals take the trouble to transcend masturbation, and engage instead with the outside world in pursuit of pleasure and relief from pain. The answer was found in the fact that a primary SEEKING instinct exists, alongside various PLEASURE-LUST instincts. This implies that masturbatory pleasure, while satisfying the second of these, leaves the first of them (the object-seeking instinct) dampened for a while but, in the final accounting, unsatisfied. All at once, this insight throws the pivotal role of the other opioid-mediated instinct, PANIC-GRIEF, into sharp relief.

As already mentioned, this system evolved in order to foster social bonds – first and foremost between infants and their mothers, then between sexual mates, and ultimately between social groups of all kinds (including families and clans). It is easy to see the adaptive advantages of such an instinct, which attaches mothers (and, to a lesser extent, fathers) to their genetic offspring, the offspring to their major sources of survival care, and genetically related conspecifics more broadly to each other. The price we have to pay for this evolutionary advantage, though, is the pain of social loss: separation distress (PANIC), sadness and despair (GRIEF). The avoidance of such pain is what keeps us together: neurochemically speaking, we cling to our mothers and lovers in order to keep our mu-opioid receptor activity contentedly high.

Now, it is of the utmost importance to note that the 'attachment' processes initiated by this instinctual system *have all the hallmarks of addiction*. Consider for a moment the following tabulation of the similarities between substance addiction/withdrawal and social attachment/loss (see Table 10.1). The analogies are extremely striking. It comes as no surprise to learn, therefore, that opiates were historically the first line of treatment for depression (for summary, see Tenore, 2008). Why, then, did we stop using them for this purpose? For the simple reason that they are so addictive!

So, *attachment is a primary form of addiction*. Anyone who has fallen in love knows the truth of this statement. Being in love with someone is almost indistinguishable from being addicted to them. This, surely then, is the major biological endophenotype that is hijacked by substance abuse.

Table 10.1: Summary of the major similarities between the dynamics of opioid dependence and key features of social attachments

SIMILARITIES BETWEEN			
OPIATE ADDICTION &		SOCIAL DEPENDENCE	
1)	Drug dependence	1)	Social bonding
2)	Drug tolerance	2)	Estrangement
3)	Drug withdrawal	3)	Separation distress
a)	PSYCHIC PAIN →	a)	LONELINESS
b)	LACRIMATION →	b)	CRYING
c)	ANOREXIA →	c)	LOSS OF APPETITE
d)	DESPONDENCY →	d)	DEPRESSION
e)	INSOMNIA →	e)	SLEEPLESSNESS
f)	AGGRESSIVENESS →	f)	IRRITABILITY

Source: Panksepp (1998)

But where does this leave Freud's claim regarding masturbation? In our opinion, it encourages us to take a deeper view of what masturbation actually entails. Although it is difficult to know what is going on in the mind of a masturbating infant (it is important to remember that Freud included pre-genital pleasures – thumb-sucking, etc – under this heading), it seems unlikely that it entails pleasurable sensations alone, devoid of representational contents. Certainly this applies to the masturbatory fantasies of adolescents and adults. What excites the pleasurable sensations is not manual stimulation alone but almost invariably the presence of an imaginary partner, or at least of another person of some kind. In short, what distinguishes masturbation from actual copulation is not so much an absence of object-seeking as a *frustration* of object-seeking. One masturbates for *lack* of an object (whatever the reason for that lack might be). This is why masturbation is considered inferior to copulation, not only by society, but by the masturbator too. Masturbation is ultimately an empty source of pleasure, in a very literal sense. Masturbation involves frustration of the SEEKING instinct, plus satisfaction of the PLEASURE-LUST instinct, which equals empty (objectless) pleasure, pleasure without attachment, or worse: substitutive pleasure in the absence of a specific longed-for object (ie, object of affection). This formulation fits perfectly with the understanding of addiction outlined above. Addiction, like masturbation, is a substitute and replacement not only for general mastery of the object world, but specifically for *the attainment of a secure love object*.

This blindingly obvious insight has massive clinical relevance, today as much as ever. Moreover, the distinction between the abuse of DA-activating substances to buttress object-seeking (to increase social confidence, etc), and the abuse of opiates to actually replace the object, suggests that the latter may be a more malignant (less hopeful) form of addiction.

Despite all Freud's quaint and sometimes misleadingly idiosyncratic language, we trust that readers will agree that his conception of addiction as *a substitute for mature sexual attachment*, and therefore an equivalent of masturbation, still describes the pivot of the problem. The deeper and more detailed insights (and potentially powerful new therapeutic tools) provided by modern neuroscientific approaches to the underlying mechanisms around which the problem of addiction revolves makes it all the more imperative that we do not lose sight of this wood for the trees. The implications of this deepening understanding apply equally to new psychological and pharmacological treatment possibilities.

Conclusion

To avoid misunderstanding, we will summarise our argument as succinctly as possible. Addiction involves (1) a primary appetitive process called SEEKING, plus (2) a primary consummatory process called PLEASURE-LUST, which rewards the SEEKING activity and thereby allows learning to occur, plus (3) a primary social process called attachment, which is mediated by the PANIC-GRIEF system. Once an attachment is established, reunion with the object of attachment is the specific pleasure that the addict seeks. Our argument is that addiction researchers who apply 'incentive salience' theory conflate 1 and 2, and they overemphasise this aspect of addiction without recognising the importance of 3, which in our view is the big-ticket item. It is the big-ticket item for the simple reason that the real object of processes 1 and 2 – what they really 'want' – is 3. Many addiction researchers today seem to think that what the addict wants is a drug (DA-mediated). We, by contrast, think that what the addict really wants is to restore lost attachments (mu opioid-mediated). The SEEKING followed by PLEASURE learning-processes that these researchers prioritise are typically in the service of this particular type of 'wanting'. In other words, addicts, like masturbators, are not really looking for a sensory reward; the substance abuse is a self-soothing substitute for what they really want.

The second of the two Freud quotes cited above ends like this:

> [The success of a treatment for addiction] will only be an apparent one, so long as the physician contents himself with withdrawing the narcotic substance from his patients, without troubling about the source from which their imperative need for it springs … Whenever normal sexual life can no longer be established, we can count with certainty on the patient's relapse. (Freud, 1898:276)

This conclusion still rings true more than a century after it was first reached. We would only add 'social attachment' – primal mother–infant bonding – to Freud's use of the term 'sexual life', since Freud implicitly included almost all other rewarding aspects of loving interaction under his broad use of the word 'sexual'.

Indeed, recent animal research has indicated that maternal CARE urges reduce the brain's tendency to find cocaine attractive (eg, Ferris et al, 2005). The substitutive attachment aspects of addiction probably go a long way to explaining why 12-step programmes are among the most effective ways to break addictive cycles. They return participants into an emotionally engaged and ultimately satisfying social network, which is so patently lacking in

the lives of many addicts. For those who seek new pharmacological therapies for addiction, we might suggest that they evaluate the paradoxical prediction (by current standards) that the non-addictive opioid receptor agonist-antagonist buprenorphine may be efficacious in reducing amphetamine and cocaine addictions.

References

Alcaro, A., Huber, R. & Panksepp, J. (2007). Behavioral functions of the mesolimbic dopaminergic system: an affective neuroethological perspective. *Brain Research Reviews*, 56(2):283–321.

Baler, R.D. & Volkow, N.D. (2006). Drug addiction: the neurobiology of disrupted self-control. *Trends in Molecular Medicine*, 12(12):559–66.

Berridge, K.C. (1996). Food reward: brain substrates of wanting and liking. *Neuroscience & Biobehavioral Reviews*, 20(1):1–25.

Berridge, K.C. (2007). The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology*, 191(3):391–431.

Berridge, K.C. & Robinson, T.E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, 28(3):309-69.

Chen, J., Chen, P. & Chiang, Y. (2009). Molecular mechanism of psychostimulant addiction. *Chang Gung Medical Journal*, 32(2):148–54.

Damasio, A. (1999). *The Feeling of What Happens: Body and Emotion in the Making of Consciousness*. New York: Harcourt Brace.

Ferris, C.F., Kulkarni, P., Sullivan, J.M., Jr., Harder, J.A., Messenger, T.L. & Febo, M. (2005). Pup suckling is more rewarding than cocaine: evidence from functional magnetic resonance imaging and three-dimensional computational analysis. *Journal of Neuroscience*, 25(1):149–56.

Freud, S. (1897). *Extracts from the Fliess Papers* (letter 79). Standard edition, vol. 1. London: Hogarth Press; pp 272–73.

Freud S. (1898). *Sexuality in the Aetiology of the Neuroses*. Standard edition, vol. 3. London: Hogarth Press; pp 263–85

Haber, S.N. & Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology Reviews*, 35(1):4–26.

Kassel, J.D. (ed.) (2010). *Substance Abuse and Emotion*. Washington, DC: American Psychological Association; pp 137–68.

Khantzian, E.J. (2003). Understanding addictive vulnerability: an evolving psychodynamic perspective (with commentaries by B. Johnson, G.F. Koob, V. Morrison, J. Panksepp & C. Yorke, and response by Khantzian). *Neuropsychoanalysis*, 5(1):5–21.

Koob, G.F. & LeMoal, M. (2001). Drug addicition, dysregulation of reward and allostasis. *Neuropsychopharmacology*, 24(2):97–129.

Johnson, B. (2008). Just what lies 'Beyond the Pleasure Principle'? *Neuropsychoanalysis*, 10(2):201–12.

Nader, M.A, Morgan, D., Gage, H.D., Nader, S.H., Calhoun, T.L., Buchheimer, N., Ehrenkaufer, R. & Mach, R.H. (2006). PET imaging of dopamine D2 receptors during chronic cocaine self-administration in monkeys. *Nature Neuroscience*, 9(8):1050–56.

Panksepp, J. (1971). Aggression elicited by electrical stimulation of the hypothalamus in albino rats. *Physiology & Behavior*, 6(4):311–16.

Panksepp, J. (1982). Toward a general psychobiological theory of emotions. *The Behavioral and Brain Sciences*, 5(3):407–67.

Panksepp, J. (1986). The anatomy of emotions. In R. Plutchik (ed.) *Emotion: Theory, Research and Experience Vol. III. Biological Foundations of Emotions*. Orlando: Academic Press; pp 91–124.

Panksepp, J. (1998). *Affective Neuroscience: The Foundations of Human and Animal Emotions*. New York: Oxford University Press.

Panksepp, J. & Moskal, J. (2008). Dopamine and SEEKING: Subcortical 'reward' systems and appetitive urges. In A. Elliot (ed.), *Handbook of Approach and Avoidance Motivation*. Mahwah, NJ: Lawrence Erlbaum Associates; pp 67–87.

Robinson, T.E. & Berridge, K.C. (2003). Addiction. *Annual Review of Psychology*, 54(1):25–53.

Rolls, E.T. (1999). *The Brain and Emotion*. Oxford: Oxford University Press.

Solms, M. & Nersessian, E. (1999). Freud's theory of affect: questions for neuroscience. *Neuropsychoanalysis*, 1(1):5–14.

Tenore, P.L. (2008). Psychotherapeutic benefits of opioid agonist therapy. *Journal of Addictive Diseases*, 27(3):49–65.

Volkow, N.D., Fowler, J.S., Wang, G.J., Baler, R. & Telang, F. (2009). Imaging dopamine's role in drug abuse and addiction. *Neuropharmacology*, 56(Suppl 1):3–8.

Volkow, N.D, Fowler, J.S., Wang, G.J., Hitzemann, R., Logan, J., Schlyer, D.J., Dewey, S.L. & Wolf, A.P. (1993). Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse*, 14(2):169–77.

Volkow, N.D., Fowler, J.S., Wang, G.J. & Swanson, J.M. (2004). Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Molecular Psychiatry*, 9(6):557–69.

Volkow, N.D., Fowler, J.S., Wang, G., Swanson, J.M., & Telang, F. (2007). Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. *Archives of Neurology*, 64(11):1575–79.

Volkow, N.D., Fowler, J.S., Wolf, A.P., Schlyer, D., Shiue, C.Y., Alpert, R., Dewey, S.L., Logan, J., Bendriem, B., Christman, D., et al. (1990). Effects of chronic cocaine abuse on postsynaptic dopamine receptors. *American Journal of Psychiatry*, 147(6):719–24.

Volkow, N.D, Wang, G., Begleiter, H., Porjesz, B., Fowler, J.S., Telang, F., Wong, C., Ma, Y., Logan, J., Goldstein, R., Alexoff, D. & Thanos, P.K. (2006). High levels of dopamine D2 receptors in unaffected members of alcoholic families: possible protective factors. *Archives of General Psychiatry*, 63(9):999–1008.

11 Decision-making and substance abuse: a South African perspective

Don Ross

Introduction

Several communities of scientists – economists and behavioural and social psychologists – model substance abuse and substance dependence as phenomena of *choice*. Although such modelling has a long tradition, with the rising importance of neuroscience and behavioural genetics, along with the ethical and policy dominance of so-called disease models of addiction, the ultimate status of choice models has lately become a matter for controversy. At the same time, the choice models used by economists and psychologists to represent addiction have undergone dramatic revisions over the past two decades.

This chapter reviews the debate over the scientific significance of choice and decision in the study of substance abuse and dependence, presenting reasons for doubting that this framework will be supplanted by neuroscience (as opposed to being complemented by it). It describes the new families of choice models applied to addiction by economists and psychologists, respectively. It explains that although these families have a common conceptual origin, they diverge in consequence of being intended to serve different practical purposes. Finally, it reviews the limited applications of these models in South Africa to date, and identifies urgent research priorities based on policy needs.

Decision, choice, substance abuse and addiction

The status of models of decision-making in the behavioural sciences is a subject of scholarly debate. A number of philosophers (though not the majority) argue that all claims about mental activity, including decision-making, are just approximate placeholders using folk concepts, which will ultimately be replaced by more precise identifications of neural mechanisms (Bickle, 1998). Others maintain that the very idea of decision-*making* implies a degree of volition in the generation of behaviour that is incompatible with the strict closure of causation under physical law (Rosenberg, 2011). Such strong philosophical theses are seldom explicitly adopted by scientists as constraints on their hypotheses. However, many scientists endorse a hazier expectation to the effect that advances in neuroscience will tend to systematically chip away at the proportion of behavioural patterns that presently lie in the domain of the sciences that study decision. The field of substance abuse and addiction has recently been the locus of a particularly pointed outbreak of the resulting cross-disciplinary turf controversy.

To frame this, I will begin with a definitional stipulation. By 'substance abuse' I refer to any consumption of drugs in patterns and at levels that typically predict harmful legal or

health consequences. This implies that, given the laws of South Africa plus facts about the health effects of legal recreational and social drugs, *any* non-medicinal drug consumption in this country, except moderate drinking of alcohol, constitutes substance abuse. This liberal definition makes it natural to ask whether there is a special line, which can be drawn on the basis of a scientific or clinical *principle*, that is crossed by *some* substance abuse that tips it over into *addiction*. (Many psychiatrists prefer the word *dependence*. However, this refers to a slightly narrower idea, linked more essentially to increasing tolerance and withdrawal.)

One tradition in psychology has consistently argued that the idea of addiction is a residue of demonic possession myths, which should be abandoned by science and by evidence-based medicine (Akers, 1991). However, in behavioural neuroscience the standard view is quite different. Here, it is generally believed that there is a neurochemically localisable pathology which is characteristic of addicts and which distinguishes them from non-addicted people who abuse substances from time to time. When this is combined with a belief that psychological patterns should ultimately be *reduced to* neuroscientific ones, the result is the view that whatever the decision sciences have to report about addiction at the present time is at best provisional and approximate, but perhaps mainly false (Churchland, 1988:43–50). Unsurprisingly, most decision scientists who study addiction disagree with this opinion.

The controversy has two main aspects. First, there are disputes over whether it is true that all addictions share a common neurochemical signature, and, if so, over the nature of the signature in question. For surveys of general strategies for identifying neurochemical bases of addiction, see Ross et al (2008, Chapter 5) and Redish et al (2008); for compendia of candidate mechanisms, see Koob (2006) and Madras et al (2006). Kincaid and Sullivan (2010) critically review the evidence for the existence of any such common signature, concluding that although every specific addiction must be manifest in some or other neurochemical state, the weight of evidence does not yet establish a general such state that underlies all addictions. Here, I will say no more about this part of the debate over the possible biological essence of addiction. The more relevant aspect of the general controversy for present purposes is the second one. The mainstream view in clinical neuroscience is that addiction should be regarded as a *disease* in the specific sense that it pushes the sufferer's behaviour outside the domain of voluntary control, that is, beyond the scope of choice and decision.

This second aspect of the debate is far more heated than the first. This is not because most scientists are strongly committed to metaphysical intuitions about 'free will' versus 'determinism'. Scientists and clinicians who insist that addiction is a disease do not, after all, generally deny that *non-addicted* substance abusers choose to indulge or abstain; so they do not take a stand against the very possibility of choice (see Chapter 17 of this volume). The strong feelings aroused by the dispute seem rather to be motivated by its ethical and legal implications. If addicts have no voluntary control over their addictive consumption, then it is pointless and cruel to punish them for it through social sanctions and the instruments of law enforcement. In the United States, where the majority of the published arguments on both sides of the controversy originate, what is also at stake is the eligibility of those substance abusers who are deemed addicted to claim insurance coverage for clinical treatment. If such eligibility were widely denied, then most existing addiction clinics and treatment programmes in the US would become financially unviable.

These pressures give rise to a war of words that spills out beyond the US and across the international scientific literature on substance abuse and addiction. In 2009, the Harvard-based research psychologist and substance abuse expert Gene Heyman published a book entitled *Addiction: A Disorder of Choice*. Heyman's subtitle is deliberately provocative. His avowed main objective is to challenge the claim of 'the disease model' that addicts are volitionally helpless in the face of the substances that are alleged to have taken over their neural reward circuits. The immediate result of his book's appearance was a verbal firestorm on the internet. The *Toronto Star*,[1] for example, built its review around the following quotations from other reviews:

> 'His argument crashes and burns,' says Tony George, the head of addiction psychiatry at the University of Toronto. 'I don't think there's [sic] too many self-respecting scholars in the addiction field who would agree with him. I'm shocked that Harvard University Press would publish that.'
>
> 'These guys – I don't know, academia, they just kind of take what they want, and they don't care about the truth, or what the studies show,' says Norman Miller, a professor of medicine at Michigan State University.
>
> 'What aspect of disease,' says Norman Hoffman, a psychology professor at Western Carolina University, 'does he not understand?'

The reader will note that this is not the tone of mutual respect to which most scientific discussions aspire. What should readers interested in the substance abuse science, treatment and policy make of it? The best way of answering this question is to describe the assumptions under which decision scientists study addiction, which lead them to doubt that at some point advances in neuroscience will make their role redundant.

Many people are surprised to discover that one of the disciplines that generates a steady stream of attention to substance abuse and addiction is economics. This is because substance abuse is an interestingly peculiar form of scarce resource consumption, which is the basic subject matter of economics. What makes addictive consumption puzzling from the economist's point of view is that it typically reduces the consumer's welfare[2] instead of promoting it. Note, however, that this is only *puzzling* given the contested assumption that the addict's consumption pattern is *chosen*. In this respect, Heyman's discussion in his book is exemplary of the core attitude shared by economists, who are in consensus about little else, on the general relationship between incentives and proximate causes of behaviour. Thus the rhetorical barrage against Heyman quoted above might be aimed at any economist who studies substance abuse and addiction.

Here is how Heyman frames the relevant idea of choice. Note first that his way of distinguishing between voluntary and involuntary behaviour has nothing directly to do

---

1 16 May 2009. Available at http://www.thestar.com/news/insight/article/635237

2 Economists generally do not judge that substance abusers reduce their welfare by reference to objective conditions such as financial security and longevity. Many substance abusers, and almost all of those commonly regarded as addicts, themselves judge that their substance consumption reduces their welfare, and show that this judgment is serious by spending resources to try to reduce or cease such consumption.

with the metaphysics of free will.[3] Rather, it is based simply on the fact that the frequency of some types of behaviour is sensitive to changes in costs and benefits while the frequency of some other types of behaviour is not. To cite one of Heyman's examples, when scorn began to be directed at male executives who made a habit of winking at their female colleagues and staff, the production of executive winks declined. By contrast, no amount of criticism directed at people who blink in sandstorms, no matter how much we wish they would keep their eyes on the camel, will produce any effect. For that one must distribute goggles. Noting this distinction does *not* rest on any underlying idea that the causes of blinks are neurological and mechanical, while the causal relationship between incentives and winks is a magical one that has no physical basis. Thinking that winks are voluntary behaviour is entirely compatible with knowing that people whose facial muscles are paralysed can't wink.

Every incentive that influences a behaviour must do so through particular causal channels. In a typical case, many such channels are available. I can reliably cause you to give me a rand by offering you my car in exchange, or pointing a gun at you and challenging you to choose between your rand or your life, or, if we're friends, telling you that I don't have the right change for the vending machine today. In each case, the change I produce in your incentives will require that your brain be in one of a restricted range of states. In each case, it must be awake. In the third case it probably needs to have been trained to process some language I know how to speak. And so on.

Heyman recognises that people would not get addicted to drugs if drugs didn't have characteristic effects on their brains – in particular, on neurotransmitter circuits that alter attention, cognition, emotional state and motor preparation, with different drugs affecting different such circuits in idiosyncratic ways. He also recognises that some brains are disposed by genetic and developmental factors to be more powerfully influenced by these neurochemical effects than others. Thus the single most useful everyday datum you could have if you wanted to predict the probability that someone has battled with, or will battle with, addiction is that they have an identical twin who has so battled.

Why, in defending such apparently sensible opinions, is Heyman viewed by eminent professors of medicine as ignorant or cavalier about the truth? They have two closely related complaints. First, he avows that the majority of addicts not only can quit or drastically cut down given adequate incentives to do so, but in fact *do* encounter such incentives before they reach the age of 40 and *do* quit or cut back. Second, in light of the fact that most addiction is voluntary in the sense that incentives influence it, he prefers that addiction not be called a disease.

To support the first belief, Heyman reports relevant epidemiological statistics. In the South African context, we must be cautioned that these are all derived from wealthy countries. However, within that restricted frame the relationships they reveal are remarkably clear. The majority of people diagnosed as addicts begin using their substance of abuse in adolescence or early adulthood. They seriously try but fail to quit 3–7 times. Then, before reaching middle age, they finally succeed in either reducing consumption to the point where

[3] I add the qualifier 'directly' here because theories of this relationship have been developed; see Dennett (2003) and Ainslie (forthcoming).

it is compatible with normal life (that is, they practise what is called 'chipping'), or stop altogether. Regression analysis performed on many large data sets shows that quantifiable changes in costs and benefits – including drug prices – are significant predictors of the exact timing of the inflection points in this typical pattern.[4] Thus addictive consumption, at least in rich countries, is demonstrably sensitive to changes in incentives.

A crucial caveat is required here. To yield these clear relationships, one must use large and randomised *community* – as opposed to clinical – samples. The samples must be large because addiction has low prevalence in any general population. The draw must be from the general population to avoid oversampling (let alone exclusively sampling) from addiction clinics, because most people who seek professional treatment for addiction are precisely those with the most intractable conditions. These are an extremely small proportion of all the addicts. They are also far more likely than others to suffer from so-called Axis-I comorbidities (depression, schizophrenia, anxiety, etc) or to exhibit psychiatrically recognised atypical personality traits (eg, high impulsivity). Many people suffering from (for example) depression appear to resort to mood-altering substances such as alcohol as self-prescribed medication for it. Because the effects of depression are often at least as aversive and harmful as those of alcohol addiction, depressed people have stronger than usual incentives to keep drinking. This pattern helps to explain the widespread belief that addiction is chronic and non-voluntary in the economist's sense. The vast majority of existing studies of addicts have used clinical samples. Indeed, until about 25 years ago *all* studies had relied on such samples. This produced an obvious selection bias: models of addiction were based on studying precisely the people least likely to be able to overcome their dependence.

Heyman's semantic preferences with respect to the word 'disease' are, I suspect, a major source of the rhetorical hornet's nest his book disturbed. One can make arguments favouring more nuanced choice of expression. 'Disease', being a term of everyday language, has no precise scientific meaning. One might therefore suggest to Heyman that it is a hopeless errand to set out to scientifically *refute* those who ascribe it to addicts. However, a counter-argument for forcing the semantic point is that it is directly connected to the underlying policy significance of the whole controversy as described above. Consider this quote from Heyman:

> Dr Enoch Gordis … a previous head of National Institute on Alcohol Abuse and Alcoholism, writes: 'the disease concept … has helped remove the stigma from a chronic disorder [alcoholism] that is no more inherently immoral than diabetes or heart disease.' Taking this argument to its logical conclusion, a group of leading addiction researchers argued (in the pages of the *Journal of the American Medical Association*) that insurance plans should provide the same coverage for heroin addiction, crack addiction and alcoholism as they do for traditional diseases such as cancer, arthritis and high blood pressure. (Heyman, 2009:90)

One need not be inclined to regard addiction as 'immoral' (I do not) or to think addiction to anything should be criminalised (I do not) in order to recognise that the policy suggested

[4] Heyman presents only a small subset of the data in question. For a more comprehensive survey, supported by theoretical discussions, see the papers collected in Vuchinich and Heather (2003).

by these researchers would give rise to what economists call a 'moral hazard' problem. Most important diseases, such as cancer, are either not subject to choice, or are 'chosen' by people only in the negative sense that they do not take diligent lifestyle precautions against them. No aspect of cancer is regarded by anyone as fun. This cannot be said about the early years or months of substance abuse for most people who engage in it. Thus where medical insurance covers the costs of addiction treatment, the people most inclined to abuse substances have motivation to buy such insurance not shared by most disease victims. Two negative social outcomes follow: rates of addiction will be higher, as will insurance premiums for purchasers of all related medical schemes. Note once again the importance of choice here: the moral hazard problem is less significant, so less is at stake in whether we think of addiction as a disease in a country with universal publicly provided health care, as opposed to a country such as South Africa which depends heavily on privately sold insurance.

These considerations notwithstanding, the decision scientist studying addiction can remain agnostic on the ultimate appropriateness or inappropriateness of the disease metaphor. Nor is the decision scientist necessarily committed to any particular psychological model of choice processes. Our interest, rather, is in certain structural relationships in patterns of consumptive choices, and in the factors – both 'internal' to the person and 'external' to him or her – that systematically predict changes in these patterns. Economists understand the factors in question as incentives – more specifically, as costs and benefits that can be weighed in terms of a standard measure of utility. In the next section I will set out the basic theoretical framework that decision scientists use for modelling the choice patterns implicated in substance abuse and addiction.

Models of substance abuse choice

Ross (2010) generalises the range of existing choice-theoretic models of substance abuse and addiction as variations on accounts of a more general range of *procrastination* phenomena. At any given point in time a person can choose actions that constitute investments in his or her longer-range welfare, or can postpone this effort until later and enjoy consumption of immediate relaxation. All substances of abuse are vehicles for such procrastination. Because being intoxicated is typically incompatible with effortful investment, people who choose to procrastinate by getting high thereby *commit* to their choice for a period of time, which, during the period of intoxication, relieves them of the anxiety of knowing they could 'get back to work' at any moment given some level of effort. Anxiety caused by a behavioural choice is a cost associated with that behaviour, so people can be expected to be attracted to mechanisms that reduce it. This is part of the pleasure of intoxication. The other main source of its pleasure lies in the action of neurochemical mechanisms, an aspect which lies outside the scope of the present topic focus (but see previous references). A property of substance addiction that is common to procrastination processes in general is that the longer a person puts off investments in the future, the higher becomes the cost of switching from procrastination to investment at any particular moment. Thus procrastination generally, and addiction specifically, have the form of 'behavioural traps'.

The choice-theoretic model of addiction from which all currently leading ones are conceptually descended is due to Becker and Murphy (1988). This is usually referred to as

the 'rational addiction' model. The basis of the label is that, according to the model, although the addict's repeated choices cause his or her welfare to steadily decline *over* time, *at* any given moment of choice the addict is best off choosing to consume the drug. Thus the addict can never be said on this model to make an irrational choice. This has struck many people as too intuitively bizarre to take seriously. However, the judgment that a scientific model or theory confounds everyday intuitions is not a substantive objection to it, since there is no reason to believe that everyday intuitions track truth (Cromer, 1995; Wolpert, 2000; Ladyman & Ross, 2007). The *sound* reason for the eclipse of the rational addiction model is that it makes a general false prediction about addicts' attitudes to relapse following periods of withdrawal. According to the model, *if* an addict successfully overcomes withdrawal *and* intended at the time of entering withdrawal to quit for good, then either he or she should never relapse or should never permanently quit. But the overwhelming majority of addicts repeatedly undergo the rigours of withdrawal, planning never to relapse, and then return to addictive consumption – before eventually quitting successfully. Thus the rational addiction model is empirically refuted by a basic aspect of the standard addictive pattern. (For the detailed logic underlying this argument, see Ross et al, 2008, Chapter 3.)

The roots of this misprediction by the rational addiction model lie in the fact that it has no device for allowing either an individual's preferences or the objects of preference to change over time. At the broadest level, we find two families of subsequent models that address this missing flexibility in different ways. Some theorists view these families as competitors between which a choice should be forced, but Ross (forthcoming) explains why we should not regard them in this way. They are better seen as complementary forms of description, each of which is useful in different applied contexts.

The first family of models has been developed by economists. What is characteristic of their approach is that they treat the *objects* of choice – eg, drug consumption or alternative activities such as working or enjoying family time – as fixed through all stages of analysis. For reasons that have partly to do with mathematical and statistical tractability, but are also related to the demands of policy domains in which we cannot, for practical or ethical reasons, discriminate among individuals, the economist's modelling strategy is most useful for generalising the costs and benefits of a form of procrastination, such as substance abuse, across *populations* of people. The approach collapses all of the specific ways in which different people idiosyncratically experience dilemmas of choice into a variable parameter that represents a cost of resisting temptation. This allows us to then represent, for purposes of empirical measurement in a given range of cases, the comparative effects of contextual factors in the environment and factors 'intrinsic' to the tempting rewards, on the cost variable. In the case of abused and addictive substances, examples of the contextual factors include monetary prices of drugs relative to budgets, expectations of social disapproval of drug consumption and intoxication,[5] risks and magnitudes of legal sanctions, and cultural expectations that normalise, to varying degrees in different environments, the social role of the substance abuser or addict.[6] Examples of the reward factors include expected health consequences, expected intensity and magnitude of highs, and anticipations of hangover and withdrawal.

[5] See Chapter 16 of this volume for discussion.
[6] See Chapter 15 of this volume for discussion.

The economic literature features a range of models in this family. Leading instances are Akerlof (1991), Laibson (1997, 1998), O'Donoghue and Rabin (2001), Gul and Pesendorfer (2001), Bénabou and Tirole (2004), Benhabib and Bisin (2004), Bernheim and Rangel (2004), and Fudenberg and Levine (2006). A main feature on which these models vary is that some of them allow for competing *decisions* made by different sub-parts of people's brains, while others treat temptations as costs that are imposed on a unitary chooser by forces from the external environment – which can include parts of a person's own brain over which the person lacks voluntary control. In other words, models of the first type treat different parts of the brain as distinct choosers, while the second type treat parts of the brain as external to the agent who makes choices. In general, these differences do not reflect divergent ideas about how the brain works. They rather represent alternative abstract *descriptions* of the relationships between relevant neural mechanisms, whatever exactly these turn out to be, and incentivising pressures and opportunities. Economics is a kind of engineering, and like other engineers economists choose descriptions that best fit practical policy alternatives. A property of all of the models cited above is that they admit of *equilibrium solutions*, that is, they allow one to look for simultaneous quantitative values of costs and benefits such that, to the extent that the model specification is approximately accurate, proportions of choices of addictive behaviour are predicted to remain *stable*. In principle, this allows policy-makers to try to influence levels and prevalence rates of substance abuse through manipulations of variables that are under their control, such as taxes on alcohol and cigarettes, penalties for possession of illegal drugs, accessibility of treatment programmes, and prices of drugs that are influenced by suppression of trafficking and revenue laundering. Of course, such control is always imperfect, but economists can factor such imperfection into their models through use of probabilistic response functions.

To date, no model in this family has been empirically estimated for any developing or poor country, such as South Africa. As I will explain in the third part of this chapter, this knowledge gap constitutes a barrier to optimal policy choice, and therefore stands as an urgent space for future research.

The second family of models, developed by psychologists and the so-called *behavioural* economists who work on the frontier between economics and psychology, is more relevant to predicting and explaining responses of individual substance abusers and addicts. Of course, insofar as individuals resemble one another, these models will also generate aggregate-level predictions, and should be at least compatible with economic models of the same groups. But the psychological models are not, like the economic models, designed with population-level estimation in mind as a goal. They primarily facilitate clinical treatment rather than public policy.

An early proponent of the psychological approach to modelling procrastination and related phenomena was the economist and Nobel laureate Thomas Schelling (1978, 1980, 1984). This approach has been most extensively developed by a group of psychologists whose intellectual roots lie in the laboratory of the late Richard Herrnstein. The group's most notable contributors, aside from Herrnstein, are George Ainslie, Leonard Green, Drazen Prelec and Howard Rachlin. Warren Bickel played a crucial early role in empirically applying their framework to specific substance addictions. Key highlights of this literature are collected as Herrnstein (1997). Seminal papers not included there are Rachlin and

Green (1972), Ainslie (1975), Loewenstein and Prelec (1992), Bickel, Madden and Petry (1998), Bickel and Marsch (2001), and Kirby and Guastello (2001). Ainslie (1992, 2001) and Rachlin (2000) provide broad-ranging general accounts of the perspective, while Ross (2005) sets it in a wider context with respect to economics and philosophy of science.

The psychological models resemble the economic ones in their core feature, inherited from the rational addiction model, of understanding addiction as a consequence of people discounting the value of future rewards by comparison with present ones. Like the current economic models, but unlike the rational addiction model, the psychological models capture the addict's tendency to repeatedly but unsuccessfully invest in quitting by allowing the rate of this intertemporal discounting to vary with distance from the reference point of current choice. The key difference is that the psychological models incorporate changes over time in people's perceptions (or 'framing') of their objects of choice. For this reason, the models cannot generally be solved by economic equilibrium analysis.

The basic, distinctive mechanism that is common to all of the psychological models works as follows. The principles for distinguishing among the actions and outcomes from which people make choices aren't fixed in cement. A person deciding between having a third drink and going to pick up the children from school can frame his or her choice as being simply between those two immediate objects. But this person could alternatively frame it as *part of* a choice between being the sort of person who would choose drinking over the family's welfare and being the sort of person who would not. This description of re-framing is 'from the outside', and doesn't require us to imagine the hypothetical decision-maker to be so self-consciously philosophical as to conceptualise his or her choice in those terms. People need merely notice that if they choose the drink today, this predicts that they will choose drinking again in similar future circumstances. Recognising this, if he or she chooses the drink he or she will suffer – in the present, not in a heavily discounted future – a dimunition in self-admiration, or self-confidence, which constitutes a current cost. In consequence, re-framing may cause the addict to perceive the costs of taking the drink as outweighing the benefits after all.

Notice that the reasoning here, cast in terms of comparative costs and benefits, is still 'economic' in the broadest sense. Indeed, it had better be, lest we find ourselves slipping into some metaphysical understanding of 'voluntary choice' that is no longer anchored to the idea of testable responsiveness to incentives. There is a particularly close relationship between Ainslie's (1992, 2001) and Prelec and Bodner's (2003) stress on present behaviour as informing the chooser about his or her probable future choices and one of the 'family 1' models, that of Bénabou and Tirole (2004), which emphasises 'self-signalling'. The key difference, however, is that Bénabou and Tirole's hypothesised chooser learns new facts only about his or her future self, whereas Ainslie's chooser learns new relationships between a succession of future selves and the structure of the world over which these selves make choices. Ainslie refers to this specific form of re-framing as 'reward bundling', or 'bundling' for short. The comparison of self-signalling with bundling nicely illustrates the respect in which the psychological models of addiction and addiction management are descriptively richer than the economic ones. This does *not* mean that the psychological models are *better* for all purposes. The very point of a modelling framework in the first place is to abstract away from the full richness of a world that is too complex to be understood merely by piling up particular observations.

As explained earlier, the psychological models are clumsy if used as guides to expected responses at the aggregate (that is, population) level to changes in variables that can be controlled by general policy. On the other hand, they have much to say about the design of treatments, which can usually be tailored to individual cases. The psychological models direct our attention especially to the following question: how can the clinician best encourage a substance abuser or addict to get into the habit of re-framing choices that he or she begins by seeing as atomic and isolated from the longer run of life? Since the psychological literature models more than one *kind* of re-framing, we should also want to know whether different styles of re-framing work better for different personalities, or for people in different kinds of family, economic or cultural circumstances.

As noted in the first section of this chapter, most substance abusers who seek treatment suffer from a co-occurring Axis I disorder such as depression, anxiety or schizophrenia. In consequence, the most common form of non-pharmacological psychological intervention against substance dependence is broad-spectrum cognitive-behavioural therapy (CBT). The practical pioneer of this approach was the South African psychologist Arnold Lazerus (1958), who has taught and practised in the United States since leaving the University of the Witswatersrand in 1966. A meta-analysis by Burke et al (2003) suggests that motivational interviewing, a form of CBT, is helpful in the treatment of substance dependence. However, several important caveats must be noted. First, CBT incorporates a very broad set of techniques, among which training in re-framing choice is only one, and one that is typically not explicitly conceptualised as such. Because of its 'broad church' character, the efficacy of CBT is difficult to test empirically, and existing literature aimed at scientific assessment is inconclusive. Second, many critics maintain that in patients with comorbid disorders including addiction, the substance abuse should be arrested by other techniques prior to beginning courses of CBT (Cohen, 1995). Third, a therapeutic focus on re-framing is best regarded as an aspect of so-called *metacognitive* therapy (Wells, 2000), which is characterised by its promoters as an *alternative* to CBT because it focuses on cognitive *processes* rather than (only) cognitive *content* (Wells & Purdon, 1999). Conceptually, however, metacognitive therapy is a refinement of CBT. Finally, it is surely an unsatisfactory state of affairs that, because most of the clinical population of substance abusers suffer from co-occurring Axis-I disorders, there is no consensus on, or even much knowledge of, which non-pharmacological interventions are most efficacious against substance abuse *by itself*. This lack of knowledge might well be one of the reasons why substance abusers without other Axis-I problems seldom seek professional help.

Direct evidence for changed choice behaviour through manipulation of intertemporal choice frames primarily consists of work with non-human animals (Ainslie, 1975; Ainslie & Monterosso, 2003). Only two studies to date, by Kirby and Guastello (2001) and Hofmeyr et al (2010), directly test the hypothesis that people can successfully be encouraged to choose in ways that suggest bundling of previously unbundled rewards. Kirby and Guastello found that experimental subjects who were forced to choose sequences of rewards were more likely to opt for larger, later rewards over smaller, sooner ones than were subjects who faced identical discrete choices at successive times. The second study, using a population of South African university students, found that regular cigarette smokers increased their proportion of less impulsive choices over a series when encouraged or forced to bundle the

rewards, whereas no such implied learning was observed in non-smoking subjects who had also been screened for other possible addictions. The authors speculatively interpret these data as suggesting that non-addicts are more likely to bundle rewards as a matter of general habit, and that this may partly explain their greater resistance to potentially addictive temptations.

Despite the shared conceptual origins of the economic and psychological models of substance abuse choice, and their common emphasis on addiction as a pathology of intertemporal reward discounting management, there is little discussion in the literature to date of ways in which researchers might use them jointly as mutual sources of specification constraint. For initial suggestions, see Ross (2005, Chapter 8) and Ross et al (2008, Chapter 8).

Studies of substance abuse choice in South Africa

To date, the economic model of addictive choice has not been estimated for any South African or developing world population. This is a major gap in knowledge. Since the models are highly sensitive to *opportunity costs* of substance abuse – that is, to the value of opportunities that substance-abusing people forego – there is no reason to expect that an estimation made on the basis of data from a wealthy country would predict anything about the expected estimation in a significantly poorer country (or, for that matter, a significantly culturally different one).

What *has* been estimated in South Africa, and in a range of other developing and poor countries, are demand price elasticities for cigarettes. That is, economists have measured the extent to which aggregate cigarette consumption changes in response to price increases driven by imposition of higher taxes. These estimations have simply used standard determinants of consumer choice, especially retail price but also per capita income, advertising expenditure by tobacco companies, firm concentration in the local tobacco industry, presence or absence of legislation aimed at restricting smoking behaviour (Van Walbeek, 2006), and estimated market share of smuggled cigarettes (Boshoff, 2008), as regressors in models with cigarette consumption as the dependent variable. This approach does not exploit the knowledge that tobacco is addictive, even in the incomplete sense of the rational addiction model, that is, it does not structurally represent the hypothesis that past consumption positively predicts future consumption independently of the other influences. A still further step would be to use one of the current, post-rational-addiction models that allow for dynamic preference change.

The failure to explicitly model addiction, at least so far, is relevant to knowledge of optimal policy. Standard economic demand modelling, as described above, has shown that, as in all populations similarly studied around the world, South African smokers choose to smoke less, and fewer South Africans choose to smoke at all, when cigarette prices increase.[7] South African demand elasticities are consistently within the general range observed for developing countries, that is, positive and higher than in developed countries. (So, consumption in

[7] Van Walbeek (2005) surveys results of studies conducted to that point, and in addition performs the most sophisticated data analysis available thus far.

poorer populations is more sensitive to changes in prices than consumption in richer populations, as intuition would expect.) Van Walbeek (2006) additionally establishes two results relevant to policy choice. First, because poorer smokers within South Africa cut back consumption in response to cigarette tax increases more sharply than wealthier smokers, public revenue enhancement through increases in such taxes is not regressive (that is, does not redistribute welfare from poorer to richer citizens). Second, and of great interest in the present context, tobacco companies in South Africa do not partly absorb tax increases through reductions in their profit margins per unit, which would partly offset the desired public health consequences of the policy. Instead, they *add* additional mark-ups to retail prices on top of the tax increases. A possible explanation of this is as follows. Price increases deter less addicted smokers first. Thus, demand elasticity falls with increased prices. (Numerous studies from around the world directly support this hypothesised relationship.) Thus, tobacco companies maximise profits by following tax increases with complementary price increases of their own, rather than by partly counteracting the increases or simply transferring them to consumers.

This evidence and the hypothesis that would explain it are good news for the compatibility of revenue enhancement and sound public health policy. However, as Van Walbeek notes, they ironically suggest that industry policy is alert to the addictive character of tobacco consumption while public policy disregards it. Holding current analyses fixed, use of a rational addiction model to estimate the data would yield recommendation of a higher optimal tax rate on tobacco products. Use of a post-rational-addiction model would imply a still-higher optimal rate, since this would increase the procrastination cost for smokers who plan to quit. Van Walbeek shows that the hypothesis that the industry takes addiction into account in setting prices while the National Treasury does not take addiction into account in calculating tax increases explains the fact that National Treasury has consistently fallen short of its declared target of 50% of the retail price of cigarettes being captured as public revenue.

This imperfect but still helpful knowledge about demand elasticity for addictive substances in South Africa is limited to tobacco. The very illegality of illicit drugs is a direct barrier to collection of the data we would require for modelling their demand characteristics. Similarly, the high volume of alcohol produced and sold through informal markets in South Africa makes demand elasticities for that widely abused substance intrinsically difficult to estimate. Boshoff (2008) argues that even in the case of tobacco demand, elasticities have been systematically overestimated due to failure to factor in increased levels of smuggling encouraged by tax increases. As Boshoff recognises, however, evidence concerning higher smuggling incidence is so far based exclusively on claims made by tobacco companies, which have a direct incentive to press such assertions and have historically done so on a consistent basis, even when complementary evidence has failed to support them (Van Walbeek, 2005).

One study is now under way in South Africa that will aim to estimate a post-rational-addiction choice model for a randomly selected population sample. A group of researchers led by the present author has recently conducted a prevalence study of gambling behaviour, based on 3 000 urban adult participants. Pathological gambling closely resembles substance dependence in its aetiology, behavioural profile and characteristic patterns of neural

activation. Ross et al (2008) indeed provide evidence in favour of regarding it as the basic model for addiction in general. Therefore, participants in the prevalence study, in addition to providing information on their gambling behaviour and completing the Pathological Gambling Severity Index (PGSI) from the Canadian Problem Gambling Inventory, also completed the WHO-ASSIST screens for alcohol and illicit drug abuse and dependence,[8] along with standard instruments for measuring depression (Beck's Depression Index), anxiety (Beck's Anxiety Index) and impulsive personality (Barratt Impulsiveness Scale). The data from this study have not yet been analysed using a choice model. However, linear regressions using PGSI and WHO-ASSIST alcohol scores, respectively, as independent variables indicate that, as in other populations similarly examined, co-occurring Axis-I disorders and being male are the most robust predictors of risk for both pathological gambling and alcohol dependence. Identification of these factors is not informative with respect to the relative impact of environmental and biological factors on the two kinds of disordered consumption. In addition, living in the West Rand, the area around Johannesburg dominated by mines, is a strongly significant predictor of both gambling and alcohol risk. This may reflect the influence of an environment dominated by men living apart from their families, socialising in mainly male groups, and having some discretionary income.[9]

The present author's group is currently studying a subset of 300 participants from the above study, whose gambling behaviour, drinking, drug use and other Axis I states are being monitored at three-monthly intervals for 18 months. At each visit, subjects participate in experiments that ask them to make choices among temporally delayed and uncertain rewards, which enable us to estimate their attitudes to risk and delay following the method of Andersen et al (2008). This is, in turn, intended to enable us, data willing, to estimate the relative proportions of risk for pathological gambling and alcohol dependence that are best predicted by rational addiction and post rational addiction models, respectively. If this experiment is successful, it will yield the first such information about a South African sample. Following completion of this longitudinal study, subjects will also participate in an experiment intended to compare dispositions to learn to bundle rewards among subjects measured as being at, respectively, low, medium and high risk for pathological gambling.[10]

At this point in time, then, it cannot be said that much is specifically known about substance abuse or substance dependence as phenomena of choice in South Africa. Clearly South African cigarette smokers, like all other populations of smokers studied, are sensitive in their nicotine consumption to changes in monetary incentives. However, because this has not been studied using a model that represents the dynamics of addiction, all that can so far be estimated quantitatively is the lower bound of this sensitivity. Meanwhile, there is tentative evidence that young South African smokers may be less likely to bundle rewards in the absence of explicit cues to do so than demographically similar non-smokers. Further

---

[8] See Humeniuk and Ali (2006) for discussion of the design and psychometric properties of these instruments.

[9] See Chapter 15 of this volume for discussion of the ways in which these common features of South African social organisation interact with substance abuse.

[10] The experimental method will combine the bundling three-condition design used in Hofmeyr et al (2010) with the method of estimating risk and time preferences described in Andersen et al (2008).

evidence on relationships between addiction and inter-temporal reward discounting and framing in South Africans is anticipated soon.

Surveying literature on substance abuse in South Africa that was available in 1998, Parry and Bennetts list the following as tentatively indicated influences on incidence, prevalence and severity:

> … socio-economic status, poverty, urbanization, delinquency, family background, peer pressure, religion, ideology, educational disturbance, truancy, availability, price, unemployment, job opportunities, anomie and alienation, tradition, legal arrangements and the enforcement of existing legislation (e.g. drinking and driving laws), and historical factors. (Parry & Bennetts, 1998:81)

Intuitively, at least half of these potential factors must operate, if they do operate, through the influence of incentives on choice. In light of the prominence of substance abuse among South Africa's major public health problems, an extensive research agenda in the area evidently lies stretched out before the country's decision scientists.

Acknowledgments

Research relevant to the writing of this chapter was supported by the South African Responsible Gambling Trust, the Center for Ethics and Values in the Sciences at the University of Alabama at Birmingham, and the National Research Foundation of South Africa.

References

Ainslie, G. (1975). Specious reward: a psychological theory of impulsiveness and impulse control. *Psychological Bulletin*, 82(4):463–96.

Ainslie, G. (1992). *Picoeconomics*. Cambridge: Cambridge University Press.

Ainslie, G. (2001). *Breakdown of Will*. Cambridge: Cambridge University Press.

Ainslie, G. (forthcoming). 'Free will' as recursive self-prediction: does a deterministic mechanism reduce responsibility?' In J. Poland & G. Graham (eds), *Addiction and Responsibility*. Cambridge, MA: MIT Press.

Ainslie G., & Monterosso, J. (2003). Building blocks of self-control: increased tolerance for delay with bundled rewards. *Journal of the Experimental Analysis of Behavior*, 79(1):37–48.

Akerlof, G. (1991). Procrastination and obedience. *American Economic Review*, 81(2):1–19.

Akers, R. (1991). Addiction: the troublesome concept. *The Journal of Drug Issues*, 21(4): 777–93.

Andersen, S., Harrison, G., Lau, M. & Rutström, E. (2008). Eliciting risk and time preferences. *Econometrica*, 76(3):583–619.

Becker, G. & Murphy, K. (1988). A theory of rational addiction. *Journal of Political Economy*, 96(4):675–700.

Bénabou, R. & Tirole, J. (2004). Willpower and personal rules. *Journal of Political Economy*, 112(4):848–86.

Benhabib, J. & Bisin, A. (2004). Modeling internal commitment mechanisms and self-control: A neuroeconomics approach to consumption-saving decisions. *Games and Economic Behavior*, 52:460–92.

Bernheim, B.D. & Rangel, A. (2004). Addiction and cue-triggered decision processes. *American Economic Review*, 94(5):1558–90.

Bickel, W., Madden, G. & Petry, N. (1998). The price of change: the behavioral economics of drug dependence. *Behavior Therapy*, 29(4):545–65.

Bickel, W. & Marsch, L. (2001). Toward a behavioral economic understanding of drug dependence: delay discounting processes. *Addiction*, 96(1):73–86.

Bickle, J. (1998). *Psychoneural Reduction: The New Wave*. Cambridge, MA: MIT Press.

Boshoff, W. (2008). Cigarette demand in South Africa over 1996–2006: the role of price, income and health awareness. *South African Journal of Economics*, 76(1):118–31.

Burke, B., Arkowitz, H. & Menchola, M. (2003). The efficacy of motivational interviewing: a meta-analysis of controlled clinical trials. *Journal of Consulting and Clinical Psychology*, 71(5):843–61.

Churchland, P. (1988). *Matter and Consciousness*. 2nd edition. Cambridge, MA: MIT Press.

Cohen, S. (1995). Alcohol and benzodiazepines generate anxiety, panic and phobias. *Journal of the Royal Society of Medicine*, 88(2):73–77.

Cromer, A. (1995). *Uncommon Sense*. Oxford: Oxford University Press.

Dennett, D. (2003). *Freedom Evolves*. London: Penguin.

Fudenberg, D. & Levine, D.K. (2006). A dual-self model of impulse control. *American Economic Review* 96(5):1449–76.

Gul, F. & Pesendorfer, W. (2001). Temptation and self-control. *Econometrica*, 69(6): 1403–36.

Herrnstein, R. (1997). *The Matching Law.* Cambridge, MA: Harvard University Press.

Heyman, G. (2009). *Addiction: A Disorder of Choice*. Cambridge, MA: Harvard University Press.

Hofmeyr, A., Ainslie, G., Charlton, R. & Ross, D. (2010). The relationship between addiction and reward bundling: an experiment comparing smokers and non-smokers. *Addiction*, 106(2):402–409.

Humeniuk, R. & Ali, R. (2006). *Validation of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) and Pilot Brief Intervention: A Technical Report of Phase II Findings of the WHO ASSIST Project.* Geneva: World Health Organization.

Kincaid, H. & Sullivan, J. (2010). Medical models of addiction. In D. Ross, H. Kincaid, D. Spurrett & P. Collins (eds). *What is Addiction?* Cambridge, MA: MIT Press; pp. 353–76.

Kirby, K. & Guastello, B. (2001). Making choices in anticipation of similar future choices can increase self-control. *Journal of Experimental Psychology: Applied*, 7(2):154–64.

Koob, G. (2006). The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. *Addiction*, 101(Suppl. 1):23–30.

Ladyman, J. & Ross, D. (2007). *Every Thing Must Go.* Oxford: Oxford University Press.

Laibson, D. (1997). Golden eggs and hyperbolic discounting. *Quarterly Journal of Economics*, 112(2):443–77.

Laibson, D. (1998). Life-cycle consumption and hyperbolic discount functions. *European Economic Review*, 42(3–5):861–71.

Lazerus, A. (1958). New methods in psychotherapy: a case study. *South African Medical Journal*, 32:660–64.

Loewenstein, G. & Prelec, D. (1992). Anomalies in intertemporal choice: evidence and an interpretation. *The Quarterly Journal of Economics*, 107(2):573–97.

Madras, B., Colvis, C., Pollock, J., Rutter, J., Shurtleff, D. & von Zastrow, M. (2006). *Cell Biology of Addiction*. Cold Spring Harbour, NY: Cold Spring Harbor Laboratory Press.

O'Donoghue, T. & Rabin, M. (2001). Choice and procrastination. *Quarterly Journal of Economics*, 116(1):121–60.

Parry, C. & Bennetts, A. (1998). *Alcohol Policy and Public Health in South Africa.* Cape Town: Oxford University Press Southern Africa.

Prelec, D. & Bodner, R. (2003). Self-signaling and self-control. In G. Loewenstein, D. Read & R. Baumeister (eds). *Time and Decision*. New York: Russell Sage Foundation; pp 277–98.

Rachlin, H. (2000). *The Science of Self-Control*. Cambridge, MA: Harvard University Press.

Rachlin, H. & Green, L. (1972). Commitment, choice, and self-control. *Journal of the Experimental Analysis of Behavior*, 17(1):15–22.

Redish, A.D., Jensen, S. & Johnson, A. (2008). A unified framework for addiction: vulnerabilities in the decision process. *Behavioral and Brain Sciences*, 31(4):415–37.

Rosenberg, A. (2011). *The Atheist's Guide to Reality: Enjoying Life Without Illusions.* New York: Norton.

Ross, D. (2005). *Economic Theory and Cognitive Science. Volume One: Microexplanation.* Cambridge, MA: MIT Press.

Ross, D. (2010). Economic models of procrastination. In C. Andreou & M. White (eds). *The Thief of Time*. Oxford: Oxford University Press; pp 28–50.

Ross, D. (forthcoming). Neuroeconomics and economic methodology. In J. Davis & W. Hands (eds). *Handbook of Economic Methodology*. London: Edward Elgar.

Ross, D., Sharp, C., Vuchinich, R. & Spurrett, D. (2008). *Midbrain Mutiny: The Picoeconomics and Neuroeconomics of Disordered Gambling*. Cambridge, MA: MIT Press.

Schelling, T. (1978). Egonomics, or the art of self-management. *American Economic Review*, 68:290–94.

Schelling, T. (1980). The intimate contest for self-command. *Public Interest*, 60:94–118.

Schelling, T. (1984). Self-command in practice, in policy, and in a theory of rational choice. *American Economic Review*, 74:1–11.

Van Walbeek, C. (2005). *The Economics of Tobacco Control in South Africa*. Doctoral dissertation, University of Cape Town. Available from: http://www.commerce.uct.ac.za/Economics/staff/cwalbeek/research.asp; accessed 1 August 2011.

Van Walbeek, C. (2006). Industry responses to the tobacco excise tax increases in South Africa. *South African Journal of Economics*, 74(1):110–22.

Vuchinich, R. & Heather, N. (eds) (2003). *Choice, Behavioral Economics and Addiction.* Oxford: Pergamon/Elsevier.

Wells, A. (2000). *Emotional Disorders and Metacognition: Innovative Cognitive Therapy.* Chichester: John Wiley & Sons.

Wells, A. & Purdon, C. (1999). Metacognition and cognitive-behaviour therapy: a special issue. *Clinical Psychology and Psychotherapy*, 6(2):71–72.

Wolpert, L. (2000). *The Unnatural Nature of Science*. Cambridge, MA: Harvard University Press.

12 Animal models of substance abuse

Vivienne A. Russell, Jacqueline Dimatelis and William M.U. Daniels

Introduction

Excessive drug intake changes natural reward and stress systems in the brain, causing a transition from positive to negative reinforcement mechanisms that drive drug-seeking behaviour (Edwards & Koob, 2010). Animal studies suggest that the transition from occasional drug intake to addiction is associated with a persistent impairment in synaptic plasticity (Kasanetz et al, 2010). The net effect of addictive substances or stress is impairment of inhibitory GABAergic synaptic plasticity, thereby increasing excitability of dopamine neurons and contributing to the early stages of drug addiction (Niehaus et al, 2010). Although animal models may not fully reproduce the human disorder, they nevertheless provide unique insights into the neural changes that occur during the three major stages of drug addiction: *binge/intoxication*, *withdrawal/negative affect* and *preoccupation/anticipation* (Koob, 2009; Koob & Volkow, 2010). For instance, it has been shown that the ventral tegmental area (VTA) of the midbrain and nucleus accumbens (ventral striatum) are key structures in the binge/intoxication stage, while the extended amygdala contributes to the stress-induced withdrawal/negative affect stage (Koob & Volkow, 2010). Similarly, preoccupation/anticipation, or craving, is produced by a widely distributed network involving the prefrontal cortex, dorsal striatum, basolateral amygdala, hippocampus and insula, while disruption of inhibitory control is mainly attributed to dysfunction of the cingulate gyrus and prefrontal cortex (Koob & Volkow, 2010). The transition to addiction involves neuroplasticity in all of these structures. It may begin with changes in the mesolimbic dopamine system, followed by a cascade of neuroadaptations from the ventral striatum to the dorsal striatum and orbitofrontal cortex, and eventually dysregulation of the prefrontal cortex, cingulate gyrus and extended amygdala (Koob & Volkow, 2010) (see also Figure 12.2 and Chapter 6).

Animals willingly perform behavioural tasks in order to obtain drugs of abuse. These tasks include drug self-administration, which provides an animal model that is predictive of drug abuse potential (Koob, 2009). Two other animal models provide indirect measures of drug reinforcement/reward by measuring reward thresholds using conditioned place preference and brain stimulation reward. The ability of drugs to decrease brain reward thresholds correlates with their abuse potential (Koob, 2009). Animal models that demonstrate the compulsive elements of the binge/intoxication stage and increased motivation to seek drugs continue to display drug-seeking behaviour despite negative or aversive consequences. Animal models of the negative-reinforcing effects of dependence, such as conditioned place aversion, elevations in reward thresholds and decreases in responding for non-drug rewards on a progressive-ratio schedule of reinforcement, provide information about mechanisms

of adaptation of the neural networks involved in motivation and learning. This chapter will review evidence to highlight the important role that animal models play in furthering our understanding of how drugs of abuse alter specific neural circuits to give rise to the addictive state (see Chapter 2 for clinical definition of abuse and dependence).

Substance abuse cannot be understood without going beyond the cortico-striato-cortical circuits that control the emotional drive for natural rewards such as food and water. Firstly, we have to understand the changes that substances of abuse produce in these reward circuits which result in addiction, the feeling of wanting, craving a drug above all else, without actually 'liking' it. The second problem is to attempt to explain the apparent loss of self-control in the compulsive and chronically relapsing drug-addicted individual. Perception of the relative value of a reward (eg, food vs drug) may be altered in drug-addicted individuals, such that the drug is perceived to be more salient than any competing stimulus. Alternatively, drug-addicted individuals may be aware of the relative importance of the stimuli but deliberately choose to satisfy their immediate pleasure-seeking drive and ignore the consequences of their action. Top-down control over their actions will depend on how far they have descended in the spiral of addiction.

The reward circuits include the VTA, the nucleus accumbens (ventral striatum), hypothalamus, prefrontal cortex (which includes the orbitofrontal cortex) and anterior cingulate cortex (Volkow et al, 2003; Sellings & Clarke, 2003). These structures form part of the limbic system of the brain, which controls mood and motivation for reward (drug-seeking behaviour). The dopamine-mediated reward pathway is fundamental to natural reward and addiction. All drugs of abuse stimulate dopamine release from terminals of dopamine neurons that project from the VTA to the nucleus accumbens (Di Chiara et al, 2004). The same neurons also project to the medial part of the prefrontal cortex to modulate neuronal signalling through cortico-striato-cortical circuits that are responsible for attributing salience to reward-predicting stimuli. Besides its role in the regulation of emotion, the prefrontal cortex is also critically involved in higher-order cognitive function, such as working memory, decision-making and inhibition of inappropriate thoughts and behaviour, as well as consolidation of long-term declarative (explicit) memory. The nucleus accumbens is connected to limbic structures such as the prefrontal cortex, dorsolateral nucleus of the thalamus, hippocampus and amygdala. It serves as the interface between limbic areas of the brain and the motor system and provides the motivation, determining the speed and accuracy of performance (Russell, 2000).

Specific molecular mechanisms underlie the transition between the different stages of drug addiction and withdrawal and are responsible for progression from tolerance to dependence, withdrawal, craving and relapse (Koob, 2009; Nestler et al, 2001). Animal models have provided insights into the mechanisms underlying these changes in brain neurocircuitry.

Animal models of substance abuse

Although animal models cannot truly reflect human disorders, they can provide insights that cannot be obtained from human studies because of the limitations of available techniques. While non-human primate brains are closer to human brains, rodent models of human

disorders have the advantage that they have simpler nervous systems, they are genetically more homogeneous, they are less expensive to maintain, greater numbers of experimental animals are available, much more is known about their neurobiology than primates, and the researcher has better control over variables such as diet, environment and learning history (Russell et al, 2005).

Three minimal criteria have to be met before an animal can be considered to be a valid model of a human disorder. Animal models are required to (1) mimic the core symptoms of the human disorder (face validity), (2) involve similar aetiololgy and underlying pathophysiological mechanisms (construct validity), and (3) predict novel treatment strategies and biological aspects of the disorder that have not been observed in humans (predictive validity) (Willner, 1986; Sagvolden et al, 2005).

Behavioural sensitisation is one of the approaches used in animal studies to investigate the neurochemical effects of drugs of abuse. Here, the animal is subjected to a series of drug administrations, usually single doses, for a consecutive number of days, followed by intermittent periods of withdrawal, while the expression of certain behavioural parameters is recorded. In studies focusing on the effects of methamphetamine (or cocaine), animals are treated with the drug for any period ranging from 5 to 30 days, while locomotor activity and stereotypy are noted. Typically, drug-treated animals will display a progressive increase in these behaviours. After a period of drug withdrawal, a much smaller dose is required to elicit the same intensity of behaviour. Drug-induced sensitisation therefore refers to the enhanced behavioural response after a delay in drug administration following a period of repeated, intermittent drug treatment. This phenomenon is considered to be related to the initial stages of drug-seeking behaviour.

The conditioned place preference test is used to assess reward-related behaviour. During this test the animal is placed in a two-chambered apparatus. The two chambers differ from each other, thereby providing two distinctive environments that enable the animal to discriminate between them. Initially the animal is allowed to move freely in the apparatus, between the two chambers, for 15–30 minutes. The time spent in each chamber is recorded to determine the preferred chamber/environment. The animal is then placed in the opposite side (non-preferred chamber) and presented with a stimulant drug. The animal forms an association between the effects of the drug and the specific environment. If the effects were pleasant and rewarding, the animal would now change its preference and spend more time in the initially non-preferred chamber.

In the self-stimulation model, an electrode is implanted into one of the brain areas involved in motivation and reward. Animals learn that pressing a lever (which applies electrical current to the electrode) generates the feeling of hedonia. Under these circumstances, drugs that positively affect motivation and the reward system of the brain (ie, drugs that have rewarding effects) will decrease the rate of stimulation sought by the subject. In general, drugs of abuse will result in a decrease in stimulation threshold because of its reinforcing properties. This model is particularly useful to assess the abuse potential of drugs, and the basal hedonic state of the subject during withdrawal when increases in stimulation thresholds can initially be expected.

Self-administration paradigms offer excellent models to study addiction. The test relies on the hedonic properties of the drug, and the subject independently controls the drug-seeking

and delivery processes. While the previously mentioned tests are more frequently used with rodents, the self-administration test works equally well with rodents and primates. For the test, the drug of interest is administered orally, or via either a chronic indwelling intracranial or intravenous catheter that facilitates the infusion of the drug into the subject. Drug delivery is usually initiated by poking a button with the nose (for rodents) or by pressing a lever (rodents and primates). The usefulness of this technique is that withdrawal and relapse can be studied more accurately in these animals. In these instances the drug is withheld following nose-pokes or lever-presses (extinction phase). Once the animal has learnt that operating the drug delivery mechanism does not lead to drug administration, subsequent relapse/reinstatement of the extinguished response can be studied. Here, environmental cues that may enhance relapse may be investigated. The ability of the self-administration model to mimic addictive behaviour has been demonstrated by Vanderschuren and Everitt (2004). These authors showed that repetitive administration of a stimulant drug to rats leads to: (1) continued drug-seeking behaviour even when the drug is no longer available; (2) high levels of motivation, where the animals display a willingness to obtain the reward at great cost (craving); and (3) ongoing consumption of drug despite the unpleasant consequences of exposure to electric shocks after receiving the reward. It is noteworthy that these behaviours were only observed after a prolonged period of drug exposure.

The animal models described above have been instrumental in providing information about the neurobiology of addiction and the pharmacological actions of drugs. Since methamphetamine and alcohol are the major substances of abuse in the Western Cape, this chapter will mainly focus on data generated by pre-clinical experiments on these drugs.

Methamphetamine

The burden of methamphetamine use remains problematic worldwide, with increases in consumption, especially among the youth, being recently reported for North America, Southeast and East Asia and Australia. South Africa is no exception, and the number of youths seeking professional help has escalated at an alarming rate since 2000 (Plüddemann et al, 2009). One of the reasons forwarded for this dramatic increase in methamphetamine use lies in the fact that it can be easily and cheaply manufactured, and hence its growing supply drives the rising demand.

Some of the immediate effects of methamphetamine include euphoria, hyperactivity, hypersexuality, reduced anxiety and cardiovascular changes, while long-term consequences may include dental decay, weight loss, psychosis and irritability. These symptoms are all complex in nature, and explaining their development at a molecular level remains a challenge. However animal models have provided useful insight into the underlying molecular mechanisms, thereby dramatically increasing our current understanding of methamphetamine-induced addiction.

Brain areas and neurocircuitry involved in methamphetamine addiction

During various stages of drug addiction, drugs of abuse induce specific neuroplastic changes at the synaptic level (Kasanetz et al, 2010). The development of these alterations over time is suggested to underlie the establishment of addictive behaviour.

Projections from the ventral tegmental area to the forebrain

Initially, a few brain areas and neurotransmitter systems are involved in eliciting the rewarding effects of drugs of abuse. The early rewarding experiences are caused by dopaminergic projections of the mesocorticolimbic system, particularly those that originate in the VTA and innervate the nucleus accumbens (see Figure 12.1), specifically the shell subdivision (Drevets et al, 1999; Bradberry et al, 2000). Another brain area that plays an important role during the acute stages of drug taking is the prefrontal cortex (Kalivas et al, 2005). The VTA is the area of the brain that is stimulated in response to motivationally relevant stimuli, ie, the drug of choice, and responds to the stimulus by releasing dopamine (Robinson & Berridge, 1993; McClure et al, 2003) in the nucleus accumbens shell, prefrontal cortex and anterior cingulate cortex (Volkow et al, 2003; Sellings & Clarke, 2003). These brain regions are activated especially if the reward is predictable (Volkow et al, 2003). They appear to determine the intensity of responding to drug stimuli (Jentsch & Taylor, 1999; Bush et al, 2000).

The shell of the nucleus accumbens receives strong reciprocal innervation from the VTA and thus aids in modulating the response to motivationally salient stimuli. This projection participates in the learning of associations between motivationally relevant stimuli and environmental perceptions (Sellings & Clarke, 2003). Dopamine release is the trigger that directs behavioural responses toward motivationally salient stimuli and leads to cellular adaptations that facilitate learning of associations between stimuli and the event (Jay, 2003).

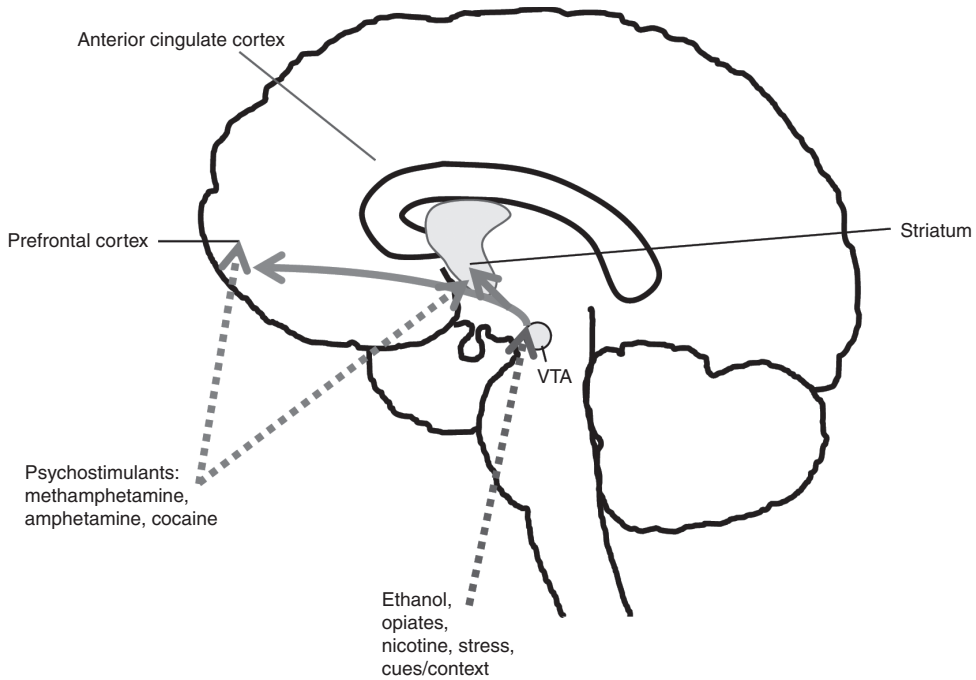

Figure 12.1: Diagram illustrating brain areas that are proposed to be affected by substances of abuse and the mesocorticolimbic dopamine projection from the ventral tegmental area of the midbrain (VTA) to the nucleus accumbens and prefrontal cortex

Interestingly, as the anticipated reward becomes fully predictable, dopamine release occurs in response to cues that predict the reward, and dopamine is no longer released upon exposure to the reward (Schultz, 1998). Drug-induced dopamine release is three to five times greater than release evoked by a natural reward (Wise, 2002). This highlights the powerful effects of drugs of abuse that contribute to the difficulty of drug cessation.

The nucleus accumbens

During the early stages of drug-taking, dopamine from the VTA and glutamate from the prefrontal cortex are released in the nucleus accumbens (Wise & Rompre, 1989). These two events are responsible for the synaptic changes in the nucleus accumbens that drive drug-seeking behaviour (Cornish & Kalivas, 2000; Kalivas & Volkow, 2005; Kalivas et al, 2005). Glutamate plays an important role in learning and neuronal plasticity. It has therefore been suggested that addiction may involve glutamate-dependent neuroplasticity in limbic cortico-striato-cortical circuits. The nucleus accumbens core is primarily involved in the expression of motivation or learned behavioural responses (Kelley, 2004; Di Ciano & Everitt, 2001) or habit learning (Ito et al, 2002). The nucleus accumbens therefore acts as an interface between motivation and action (Russell, 2000).

The amygdala

Some studies suggest that reinstatement of drug-seeking also requires the release of dopamine in the amygdala (See et al, 2001; McFarland et al, 2004). The amygdala functions in the recognition of cues that are associated with the drug or with consumption of the drug. This brain area plays a primary role in conditioned associations and the learning of these associations (Everitt et al, 2003). In order for learned associations to influence future behavioural responses, glutamatergic neurotransmission from the basolateral amygdala to the prefrontal cortex and nucleus accumbens is necessary (Cardinal et al, 2002), since rats with lesioned basolateral amygdala were unsuccessful in establishing cue-induced cocaine seeking (Whitelaw et al, 1996).

Frontal cortical areas

The frontal and prefrontal brain areas are primarily involved in executive functioning, which includes higher-order cognition, motivational functions, memory, impulse control, problem solving and decision-making (Royall et al, 2002). The frontal cortex suppresses inappropriately fast behavioural responses in order to allow slower decision-making processes to direct behaviour (Friedman & Miyake, 2004). Some of the frontal brain areas that are compromised in addiction include the dorsolateral prefrontal cortex, the orbitofrontal cortex, the anterior cingulate cortex and the ventromedial cortex. The orbitofrontal cortex is associated specifically with assessing reward value and reinforcing properties, which include the processing of short- and long-term gains or losses (Bechara, 2001; Rolls, 2000). The anterior cingulate cortex has been implicated in error processing, learning from mistakes (Bush et al, 2000), cognitive control of behaviour and emotional processing (Vogt et al, 1992; Bush et al, 2000).

In a recent study by Faure et al (2009), the authors applied proteomic techniques (2D-gel electrophoresis coupled to ESI-QUAD-TOFF mass spectrometry) to show that methamphetamine induces significant changes in the expression of a number of proteins

occurring in both the membrane and cytosol. These changes reflected alterations in cellular processes that included protein degradation, redox regulation, neuroplasticity, cytoskeletal modifications and synaptic function.

Pallidal structures

The ventral pallidum forms part of the limbic cortical-ventral striatopallidal circuitry that is implicated in drug seeking and reinstatement. The ventral striatopallidal system plays a major role in translating a motivational state into behavioural output (Kelley & Berridge, 2002; Kelley, 2004). The ventral pallidum receives input from the nucleus accumbens, midbrain, amygdala and prefrontal cortex (Napier & Mitrovic, 1999). In general, behavioural output is orchestrated by the shell of the nucleus accumbens via the ventral pallidum and mediodorsal thalamus to motor areas. This circuit usually drives the execution of behaviour in response to rewarding stimuli (Waraczynski, 2006). The nucleus accumbens shell also connects to the hypothalamus via the ventral pallidum, and this projection serves to modulate responding to natural rewards (Kelley, 2004). The ventral pallidum may therefore be seen as a relay centre for the execution of behavioural responses to rewarding or reinforcing stimuli.

The hippocampus

The hippocampus is involved in memory consolidation and is instrumental in forming learned associations necessary for the development of addiction. The hippocampus is involved in conditioning to contextual or spatial stimuli, unlike the amygdala, which is more involved in conditioning to discrete stimuli (McDonald & White, 1993). Theta burst stimulation of the hippocampus has been demonstrated to reinstate extinguished cocaine-seeking behaviour which occurred only during increased glutamate neurotransmission in the VTA. This increase in neuronal activity has been correlated with context-dependent reinstatement of drug taking (Vorel et al, 2001). Reinstatement or relapse has been closely linked to craving, and memory consolidation needed for craving is thought to be mediated by the hippocampus in conjunction with the amygdala (Hyman & Malenka, 2001).

The effects of methamphetamine on neurotransmission

The dopaminergic system

Methamphetamine affects various neurotransmitter systems involved in reward and addiction. Initially, methamphetamine affects dopaminergic pathways in order to elicit rewarding or reinforcing effects. However, this subsequently also alters neurotransmission in various other neurotransmitter pathways (Di Chiara et al, 2004; Pierce & Kumaresan, 2006). Methamphetamine acts by entering the neuron by means of the dopamine transporter (DAT), which is located in the surface membrane of the neuron. In doing so, it reverses the function of the transporter (Zahniser & Sorkin, 2004; Wilhelm et al, 2006) and acts as an ion channel leading to non-exocytotic amine release. This increases the extracellular availability of dopamine.

Methamphetamine also affects dopamine concentrations by reversing the function of the vesicular monoamine transporter 2 (VMAT2) (Wilhelm et al, 2004; Sulzer et al, 2005). The VMAT2 transporter is responsible for the intracellular vesicle storage of dopamine, serotonin, norepinephrine and histamine (Weihe & Eiden, 2000). Heterozygous VMAT2

knockout mice display enhanced methamphetamine-induced neurotoxicity (Fumagalli et al, 1999), while improved VMAT2 function reduces extracellular dopamine concentrations and its related neurotoxic effects (Vergo et al, 2007).

The enzymes responsible for the intracellular and extracellular breakdown of monoamines, monoamine oxidase (MAO) and catechol-O-methyltranferase (COMT), are inhibited by methamphetamine (Kita et al, 1995). The suppressing effect of methamphetamine on these enzymes further increases the concentration of monoamines at the synapse.

The intensity of the effects of methamphetamine was found to be directly related to greater extracellular dopamine concentrations and the occupancy of dopamine type 2 receptors (DRD2) (Volkow et al, 1999; Drevets et al, 2001). DRD2 are highly expressed in the striatum and shell subdivision of the nucleus accumbens (Larson & Ariano, 1995).

The serotonergic system

Various other transmitter systems play modulatory roles in the reward circuitry. These include serotonin (5-HT), glutamate and gamma-aminobutyric acid (GABA). The 5-HT system is ideally situated for its role as a modulator of dopaminergic activity, since the 5-HT neurons in the dorsal and median raphe nuclei innervate dopaminergic neurons in the nigrostriatal and mesolimbic systems (Phelix & Broderick, 1995; Di Giovanni et al, 2010). Serotonin has been shown to increase the inhibitory effect of dopamine on dopaminergic VTA neurons (Brodie & Bunney, 1996), resulting in decreased dopaminergic neurotransmission. Di Matteo et al (2001) have shown that 5-HT2C receptors inhibit mesolimbic dopamine function.

Serotonin plays an important role in drug reinforcement, since mice deficient in 5-HT demonstrate increased self-administration of cocaine when compared to normal mice (Parsons et al, 1998). In addition, agonists of the 5-HT2C receptor and inhibitors of the serotonin transporter decrease the firing rate of VTA dopaminergic neurons, resulting in reduced dopamine concentrations in the nucleus accumbens (Di Mascio et al, 1998; Di Matteo et al, 2000).

The 5-HT2C receptors are located on GABAergic neurons, and effects orchestrated by serotonin are proposed to be mediated by increased GABA inhibitory action on VTA dopaminergic neurons (Eberle-Wang et al, 1997). The 5-HT6 receptors expressed in the limbic and motor brain areas (Ruat et al, 1993) have also been implicated in amphetamine-induced behaviour: for example, pre-treatment with the novel 5-HT6 receptor antagonist, SB 258510A, dose-dependently enhanced amphetamine's reinforcing effects and increased extracellular dopamine concentrations in the frontal cortex (Frantz et al, 2002). Behavioural and locomotor activities induced by methamphetamine that were prevented by DAT inhibitors or the deletion of the DAT gene coincided with the release of 5-HT via the serotonin transporter (Torres et al, 2003).

Activation of other serotonergic receptor subtypes had mixed effects on the central dopaminergic system. For example, stimulation of 5-HT1B receptors reduced GABA inhibitory action in the VTA (Cameron & Williams, 1994), thereby indirectly stimulating dopamine release. In contrast, antagonism of the 5-HT2A receptor, via the selective 5-HT2A antagonist, SR46349B, decreased amphetamine-induced dopamine release in the nucleus accumbens and striatum (Porras et al, 2002).

The glutamatergic system

In general, glutamate has an excitatory effect on dopaminergic neurons in the VTA, usually leading to enhanced mesocorticolimbic dopaminergic activity. Animal studies have confirmed a role for the glutamatergic system in the rewarding effects of psychostimulants (Pierce et al, 1996; Cornish & Kalivas, 2000; Kalivas et al, 2003; McFarland et al, 2003). Acute effects of cocaine administration have been found to enhance nucleus accumbens, VTA and prefrontal cortex glutamate levels (Kalivas & Duffy, 1995; Pierce et al, 1996; Reid et al, 1997), while chronic exposure to cocaine resulted in decreased extracellular nucleus accumbens glutamate concentrations (Keys et al, 1998). Moreover, chronic cocaine administration reduced metabotropic glutamate receptor 2 or 3 (mGluR2/3) autoreceptor function in the nucleus accumbens (Xi et al, 2002), which was proposed to be a compensatory mechanism to decrease extracellular glutamate levels (Dackis & O'Brien, 2003). In line with this evidence, administration of a mGluR2/3 agonist decreased both dopamine and glutamate release in the nucleus accumbens, striatum and the prefrontal cortex, while activation of mGluR7 receptors inhibited cocaine reinstatement of drug-seeking behaviour by a mGluR2/3 mechanism in the nucleus accumbens, and antagonists of the mGluR5 and N-Methyl-D-Aspartate (NMDA) receptor decreased cocaine reward (Pulvirenti et al, 1997; Hu et al, 1999; McGeehan & Olive, 2003; Li et al, 2010; Jin et al, 2010). Also, mGluR5-deficient mice did not acquire intravenous cocaine self-administration (Karler et al, 1998), thereby supporting an important function of metabotropic glutamate receptors in cocaine-induced effects.

Interestingly, the administration of N-acetylcysteine (NAC) normalises glutamate concentrations in cocaine-pretreated rats and prevents cocaine-induced drug reinstatement in these animals. Apparently, this is achieved by restoring the cysteine/glutamate exchanger (Xi et al, 2002; Baker et al, 2003). However, the therapeutic mechanism of action has been questioned, since NAC does not cross the blood–brain barrier. NAC has a negatively charged carbonyl group, which is repelled by the negatively charged surface area of the endothelial cells of the blood–brain barrier (De Boer & Gaillard, 2006).

NMDA receptors can be activated by binding of glutamate to the NR2 subunit (Laube et al, 1997), and by binding of d-serine or glycine to the NR1 subunit (Johnson & Ascher, 1987). Glutamatergic transmission from the prefrontal cortex to the nucleus accumbens, amygdala and VTA, together with activation of NMDA receptors in these areas, have been proposed to be instrumental in the development of conditioned place preference and behavioural sensitisation induced by methamphetamine administration (Wolf, 1998). The glycine transporters are essential in the regulation of glycine levels at synapses. Antagonists of the glycine transporter inhibited glycine uptake and enhanced NMDA receptor function (Bergeron et al, 1998; Kinney et al, 2003). It would seem that glycine enhances glutamatergic neurotransmission, and therefore glycine administration may be therapeutic. This suggestion may be feasible since the glycine transporter gene has been suggested to contribute to the vulnerability to methamphetamine dependence and psychosis (Bousman et al, 2009).

The Gamma-Aminobutyric Acid (GABA) system

GABA, an inhibitory amino acid, modulates the release of basal dopamine and glutamate (Dewey et al, 1992) and has therefore been implicated in the effects of psychostimulants

(Cousins et al, 2002). The GABA-A1 and G2 receptors (GABRA1, GABRG2) have been associated with methamphetamine abuse and abuse/dependence, respectively (Bousman et al, 2009). VTA dopamine activity is modulated by GABAergic interneurons (Steffensen et al, 1998), and a major portion of nucleus accumbens efferents are GABAergic. These fibres are thought to regulate dopaminergic input from the VTA to the nucleus accumbens (Kita & Kitai, 1988).

On the other hand, cocaine and amphetamine both decrease GABAergic activity in the striatum, and this effect is mediated by DRD2 dopamine receptors (Centonze et al, 2002). A number of drugs that have their effects on GABA metabolism have been tested in substance abuse. The idea is to inhibit GABA-transaminase, an enzyme that metabolises GABA, thereby increasing synaptic GABA levels (Kushner et al, 1999). Vigabatrin (gamma-vinyl-GABA), an irreversible GABA-transaminase inhibitor, has been shown to prevent stimulant-induced dopaminergic increases in the nucleus accumbens and corticomesolimbic system, leading to an attenuation of drug-induced rewarding effects (Gerasimov et al, 1999). Similarly, topiramate, a drug that potentiates GABAergic transmission, enhanced cocaine abstinence (Kampman et al, 2004).

The noradrenergic system

It is suggested that the reinforcing effects of substances of abuse are not induced by increases in dopamine concentrations alone, since dopamine receptor antagonists do not inhibit the subjective effects caused by cocaine or amphetamine administration (Brauer & De Wit, 1997). Amphetamines and cocaine release norepinephrine more potently than they release dopamine and serotonin (Rothman et al, 2001). These increases in norepinephrine have been shown to contribute to the subjective effects of stimulants. The locus coeruleus has projections to the VTA and has the ability to influence the activity of dopaminergic neurons. For example, lesions of the locus coeruleus reduce nucleus accumbens dopamine levels (Lategan et al, 1990; Grenhoff et al, 1993), while norepinephrine depletion in the prefrontal cortex results in decreased amphetamine-induced conditioned place preference (Ventura et al, 2003). Interestingly, dopamine is taken up by both dopaminergic and noradrenergic neurons, and hence inhibition of norepinephrine transporters increases extracellular dopamine (Carboni et al, 1990; Reith et al, 1997), an effect which may enhance addictive behaviour. It is proposed that cocaine, which is an inhibitor of the norepinephrine transporter (Eshleman et al, 1999) would inhibit dopamine uptake into norepinephrine neurons, resulting in increased extracellular dopamine and concomitant reinforcement of cocaine effects (Rothman et al, 2001). These findings therefore caution against the use of drugs that act on the norepinephrine transporter, such as atomoxetine, which is often used in the treatment of attention-deficit hyperactivity disorder (ADHD).

Methamphetamine-induced neurotoxicity

One of the major contributing factors to methamphetamine toxicity is the fact that methamphetamine has a very similar chemical structure to that of the body's naturally occurring dopamine, and this allows methamphetamine to enter axons (Iversen, 2006). Toxicity occurs as a result of both endogenous dopamine accumulation and high extracellular dopamine levels released from nerve terminals (Krasnova & Cadet, 2009).

Accumulated dopamine rapidly auto-oxidises and results in the formation of oxygen free radical species, which include superoxide radicals, hydroxyl radicals, hydrogen peroxide and dopamine quinones (Acikgoz et al, 1998; LaVoie & Hastings, 1999; Miyazaki et al, 2006). In addition, it has been shown that methamphetamine can reduce the activity of copper/zinc-superoxide dismutase (CuZnSOD), and the levels of glutathione and peroxiredoxins. These observations were accompanied by high levels of lipid peroxidation and protein carbonyls (Harold et al, 2000; Gluck et al, 2001; Iwazaki et al, 2006; Li et al, 2008). When the production of reactive oxygen species overrides the anti-oxidant capacity of the cells, methamphetamine-induced terminal degeneration and neuronal apoptosis occur (Potashkin & Meredith, 2006).

Glutamate also contributes to methamphetamine-induced neurotoxicity in striatal dopamine terminals, since methamphetamine results in an increased release of glutamate in the brain (Abekawa et al, 1994; Mark et al, 2004), whereas glutamate receptor antagonists decrease methamphetamine-induced degeneration of dopamine terminals in various brain areas (Fuller et al, 1992; Battaglia et al, 2002). In general, glutamate acts via NMDA receptors to generate reactive oxygen species such as nitric oxide (Gunasekar et al, 1995), to induce cellular damage.

Oxidative stress resulting from methamphetamine administration also impairs the integrity of the blood–brain barrier (Plateel et al, 1995). For instance, methamphetamine treatment leads to the accumulation of immunoglobulins (IgG) in the amygdala and hippocampus of hyperthermic mice (Bowyer & Ali, 2006) and dysregulates the expression of tight junction proteins such as ZO-1, JAM-2, to facilitate the migration of immune cells across the blood–brain barrier (Mahajan et al, 2008). Zhang et al (2009) also demonstrated that methamphetamine results in a loss of blood–brain barrier permeability to human brain microvascular endothelial cells.

Furthermore, methamphetamine reduces glutathione levels, which are detrimental to cells (Zhang et al, 2009). Glutathione is an intracellular thiol and acts as a scavenger of reactive oxygen species (Akca et al, 2005). Glutathione therefore reduces oxidative stress (Yamamoto & Zhu, 1998) and is critical for maintaining the integrity of membranes, including the blood–brain barrier (Agarwal & Shukla, 1999). Also, when glutathione is depleted, it leads to a reduction in protein sulfhydryls, which are important for membrane function (Agarwal & Shukla, 1999). On the other hand, NAC has been shown to increase glutathione levels (Chen et al, 2008), and this may be another mechanism for NAC-induced neuroprotection. In addition, reactive oxygen species increase P-glycoprotein (Ziemann et al, 1999; Hirsch-Ernst & Kietzmann, 2000), which is a multidrug-resistance protein, located in the blood–brain barrier and expressed in endothelial cells (Demeule et al, 2000). This positioning of P-glycoprotein allows the protein to act as an efflux transporter which limits the uptake of drugs from the blood into the brain. P-glycoprotein expression is increased by glutathione depletion-induced oxidative stress in microvessel endothelial cells of rats (Hong et al, 2006). Similarly, NAC decreases P-glycoprotein upregulation induced by diethyl maleate (Wu et al, 2009). Since NAC increases glutathione levels (which protects against the oxidative stress induced by methamphetamine) and decreases P-glycoprotein efflux functionality, administration of this compound may prevent reinstatement or drug seeking in addicts.

Alcohol

Alcohol abuse is another major problem in South Africa. Ethanol addiction is a progression from occasional, impulsive use to compulsive drinking characterised by repeated cycles of withdrawal, craving and relapse. Comparable to methamphetamine, these transitional stages basically involve four overlapping circuits: (1) the reward pathway, involving the VTA, nucleus accumbens and ventral pallidum; (2) brain circuits that provide motivation and/or drive, including the orbitofrontal cortex; (3) brain circuits that produce learning and memory, requiring the amygdala and hippocampus; and (4) brain circuits responsible for cognitive control of behaviour, involving the prefrontal cortex and cingulate cortex (Kalivas & Volkow, 2005; Volkow & Li, 2005; Vilpoux et al, 2009).

Ethanol effects on dopaminergic and glutamatergic systems

Ethanol intake during the juvenile/adolescent period was shown to increase subsequent ethanol intake (Pascual et al, 2009). Rat pups, at 25 days of age, and adult rats were given injections of 25% (v/v) ethanol (3 g/kg, i.p.) in isotonic saline, or saline, on two consecutive days, followed by two days without injections, for a period of two weeks. Multiple doses of ethanol produced similar prolonged increases in dopamine concentration in the nucleus accumbens of adolescent and adult rats (Pascual et al, 2009). However, treatment with ethanol decreased expression of dopamine receptors (DRD1, DRD2) and decreased phosphorylation of the NR2B subunit of the glutamate NMDA receptor in the prefrontal cortex and striatum of adolescent animals but not of adult rats. Consistent with these findings, microinjections of DRD1, DRD2 or glutamate AMPA receptor antagonists into the nucleus accumbens attenuated drug-seeking behaviour (Anderson et al, 2006; Cornish et al, 1999; Cornish & Kalivas, 2000).

In contrast, Wang et al (2007) reported increased phosphorylation of the NR2B subunit of the NMDA receptor in the dorsal striatum following alcohol exposure that was associated with long-term facilitation (LTF) of the activity of NR2B-containing NMDA receptors in the dorsal striatum. These changes were not observed in the ventral striatum (nucleus accumbens). Further evidence supporting a role for the dorsal striatal NR2B receptor subunit in alcohol addiction was provided by the fact that dorsal, but not ventral, striatal infusion of a NR2B inhibitor reduced self-administration of ethanol in rats (Wang et al, 2007).

Chronic administration of ethanol (10% in drinking water for 12 weeks) increased NR1, NR2B and NR2C protein density in rat hippocampus but not in the frontal cortex (Bhupanapadu Sunkesula et al, 2008). Treatment of cultured cortical neurons with ethanol for five days increased NR1 and NR2B expression (Qiang et al, 2007; Qiang & Ticku, 2005), FosB protein and AP-1 promoter activity (Qiang et al, 2007), providing further support for a role for the NR2B subunit of NMDA receptors in alcohol abuse. Expression of c-Fos is under the control of NMDA receptors via the extracellular signal-regulated kinase (ERK) pathway (Lu et al, 2006; Valjent et al, 2004). Drug-induced alterations in the ERK signalling pathway in the mesocorticolimbic dopaminergic system have been suggested to contribute to the drug's rewarding effects (Zhai et al, 2007).

Epigenetic effects of ethanol

Multiple doses of ethanol during adolescence also increased acetylation of histones H3 and H4 in the frontal cortex and nucleus accumbens, while decreasing H3 and H4 acetylation in the dorsal striatum (Pascual et al, 2009). Increased histone acetylation is associated with DNA relaxation and elevated transcriptional activity, while decreased histone acetylation results in tighter DNA coiling and gene silencing, and thus serves to perpetuate altered gene expression. These findings led the authors to suggest that abnormal plasticity in reward-related processes and epigenetic mechanisms could contribute to the vulnerability of adolescents to alcohol addiction, which is consistent with the fact that brain regions that underlie attention, reward evaluation, affective discrimination, response inhibition and goal-directed behaviour undergo structural and functional reorganisation throughout late childhood and early adulthood (Pascual et al, 2009).

Ethanol and stress

Increased brain reward thresholds and increases in anxiety-like behaviour have been shown to persist after acute withdrawal in animals, mimicking protracted abstinence in human addicts (Koob, 2009; Koob & Volkow, 2010). Acute stressors have been shown to reinitiate alcohol-seeking behaviour in animals, which may result from cue- and/or stress-related neurotransmitters, orexin/hypocretin and corticotrophin-releasing factor (CRF), modulating excitatory synaptic transmission in the VTA (Bonci & Borgland, 2009; Koob & Volkow, 2010). Stephens and Duka (2008) reported that rats exposed to intermittent episodes of alcohol consumption and withdrawal were impulsive and displayed impairments in aversive conditioning. These behavioural changes were accompanied by facilitated excitatory neurotransmission and reduced neural plasticity, evidenced by decreased long-term potentiation (LTP) in the amygdala and hippocampus. The impaired LTP was accompanied by impaired associative learning and inappropriate generalisation of previously learned associations (Stephens & Duka, 2008). Stephens and Duka (2008) proposed that repeated episodes of withdrawal from alcohol (rather than ethanol intake) induced aberrant neuronal plasticity that resulted in altered cognitive and emotional competence (Stephens & Duka, 2008). A negative emotional state (anxiety, dysphoria, irritability) is produced by activation of stress systems in the brain (CRF) during acute withdrawal of all types of drugs (Koob & Volkow, 2010).

Molecular adaptations to drugs of abuse

Drug addiction depends on molecular and cellular adaptations that lead to persistent changes in transcription, translation and synaptic morphology that are enduring (Koob, 2009; Nestler, 2004; Nestler et al, 1999). The stability of some of these adaptations led to the hypothesis that long-term plasticity is an important underlying mechanism involved in these persistent modifications (Nestler et al, 1999; Vilpoux et al, 2009). The transition to addiction that defines the shift from occasional, controlled drug use to compulsive drug-taking, is associated with suppression of long-term depression (LTD) of synaptic transmission in the nucleus accumbens core, suggesting that the transition to drug addiction may be mediated by an inability to engage active processes to allow control of drug intake (Kasanetz et al, 2010)

Regulation of gene expression is considered to be a plausible mechanism of drug addiction, given the stability of behavioural abnormalities that define the addicted state (Nestler, 2008). Among many transcription factors known to influence the addiction process, one of the best characterised is ΔFosB, which is induced in the brain's reward regions by chronic exposure to virtually all drugs of abuse and mediates sensitisation to these drugs.

ΔFosB is encoded by the *fosB* gene. The immediate early genes of the fos family encode nuclear proteins (c-Fos, FosB) that form heterodimers with the Jun family proteins (c-Jun, JunB, JunD) to form the AP-1 transcription factors that bind to the promoter region of numerous genes to either activate or repress their transcription. The Fos family of proteins are induced rapidly and transiently in limbic areas of the brain following acute administration of several drugs of abuse (Nestler et al, 2001; Nestler, 2008). All of these Fos family proteins, however, are highly unstable and return to basal levels within hours of drug administration (Nestler, 2008). Very different responses are seen after chronic administration of drugs of abuse. Biochemically modified isoforms of ΔFosB (Mr 35–37 kD) accumulate within the same brain regions after repeated drug exposure, whereas all other Fos family members show tolerance, ie, reduced induction compared with initial drug exposures (Chen et al 1997; Hiroi et al 1997).

ΔFosB dimerises predominantly with JunD to form an active and long-lasting AP-1 complex (Chen et al, 1997; Hiroi et al, 1997), which can act as a transcription activator or repressor. ΔFosB binds to a gene (eg, cyclin-dependent kinase 5, cdk5) and recruits histone acetyltransferases that acetylate nearby histones and promote transcription, whereas ΔFosB binding to, for example, the c-fos gene, causes recruitment of histone deacetylases, which remove the acetyl group from histones and silence gene transcription (Nestler, 2008). As a result of its stability, the ΔFosB protein persists in neurons for several weeks after cessation of drug exposure (Nestler, 2008). The stability of the ΔFosB isoforms provides a novel molecular mechanism by which drug-induced changes in gene expression can persist despite relatively long periods of drug withdrawal. Nestler (2008) proposed that ΔFosB functions as a sustained 'molecular switch' that helps initiate and then maintain an addicted state (see Figure 12.2; Nestler et al, 2001). Consequently, drug-induced regulation of c-Fos expression could play a role in the long-term cellular adaptations that are induced by drug abuse (Vilpoux et al, 2009).

Evidence in support of this proposal was provided by bitransgenic mice in which ΔFosB had been selectively induced in the dynorphin-containing GABAergic medium spiny neurons of the nucleus accumbens and dorsal striatum (Kelz et al, 1999; Nestler 2008). Mice overexpressing ΔFosB displayed increased locomotor responses to cocaine (Kelz et al, 1999) and enhanced sensitivity to the rewarding effects of cocaine and morphine (Nestler, 2008). Specific targeting of ΔFosB overexpression to the nucleus accumbens yielded similar results, which indicated that this particular brain region could account for the phenotype observed in the bitransgenic mice (Nestler, 2008).

Mice overexpressing ΔFosB worked harder to self-administer cocaine in progressive ratio self-administration assays, suggesting that ΔFosB may sensitise animals to the incentive motivational properties of cocaine and thereby lead to a propensity for relapse after drug withdrawal (Nestler, 2008). Mice that overexpresssed ΔFosB displayed increased anxiolytic effects in response to alcohol, a phenotype that has been associated with increased alcohol intake in humans (Nestler, 2008). These findings suggest that ΔFosB, in addition to increasing sensitivity to drugs of abuse,

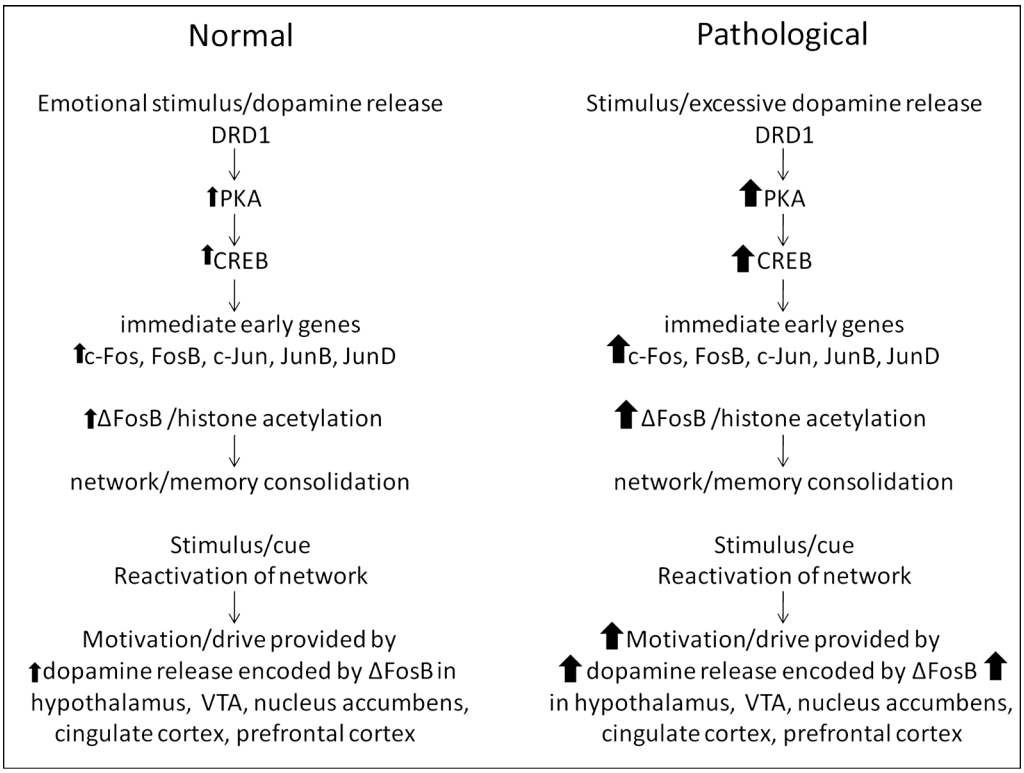

Figure 12.2: Schematic representation of the normal sequence of events following presentation of an unexpected reward giving rise to dopamine release and activation of dopamine D1 receptors (DRD1)

Notes: DRD1 activate adenylyl cyclase to give rise to cAMP formation and activation of protein kinase A (PKA). PKA, in turn, phosphorylates and activates cAMP-response-element binding protein (CREB), a transcription factor that promotes transcription of immediate early genes (c-fos, fosB, c-jun, junB, junD) and synthesis of transcription factors (c-Fos, FosB, c-Jun, JunB, JunD). FosB is encoded by the fosB gene and it, in turn, encodes an individual's exposure to emotional stimuli, both positive and negative, integrated over relatively long periods of time (Nestler, 2008). Gene transcription and protein synthesis are required for memory consolidation, long-term facilitation of transmission in reward-related neural circuits. Upon subsequent presentation of a reward-related stimulus/cue, the network will be reactivated and the motivation/drive to carry out the action will be provided by the amount of dopamine released in the nucleus accumbens which in turn is determined by the balance of proteins expressed in response to the elevated levels of FosB and other transcription factors in limbic areas of the brain.

produces qualitative changes in behaviour that promote drug seeking, and support the view that ΔFosB functions as a sustained molecular switch for the addicted state (Nestler, 2008).

Target genes of ΔFosB include GluR2, an AMPA receptor subunit (Kelz et al, 1999) that decreases permeability to calcium ions and alters postsynaptic signalling by AMPA receptors. Addictive drugs cause a rapid and persistent potentiation of AMPA-mediated synaptic responses in the VTA (Bonci & Borgland, 2009) by increasing GluR2-lacking AMPA receptors at all glutamate synapses on VTA dopamine neurons (Good & Lupica, 2010). ΔFosB overexpression in response to chronic stress or in inducible bitransgenic mice increased GluR2 expression in the nucleus accumbens and decreased the responsiveness

of the GABAergic medium spiny neurons to glutamate (Nestler, 2008; Vialou et al, 2010). Nestler (2008) hypothesised that ΔFosB levels in the nucleus accumbens represent a readout of an individual's exposure to emotional stimuli, both positive and negative, integrated over relatively long periods of time. Under normal circumstances, induction of moderate levels of ΔFosB by rewarding or aversive stimuli would be adaptive by enhancing an animal's adjustment to environmental challenges (Nestler, 2008). Higher levels of emotional stimulation would induce greater amounts of ΔFosB in nucleus accumbens neurons, altering their function so that they become more sensitive to rewarding stimuli. In this way, induction of ΔFosB would promote reward-related memory formation in response to afferent input to the nucleus accumbens.

An entirely new direction proposed for the treatment of drug addiction is based on the finding that cocaine induces expression of miRNA-212, a small non-coding microRNA that blocks gene transcription and inhibits transition from occasional drug use to uncontrolled drug intake (Hollander et al, 2010). Hollander and co-workers (2010) showed that cocaine intake increased expression of miRNA-212 in the dorsal striatum of rats, which decreased their response to the motivational properties of cocaine by amplifying the stimulatory effects of cocaine on signalling by the cyclic AMP response element binding protein, CREB. This action occurred through miR-212-enhanced Raf1 activity, resulting in adenylyl cyclase sensitisation and increased expression of the essential CREB co-activator TORC, a transducer of regulated CREB, which in turn regulates transcription of miRNA-212 and limits cocaine intake (Hollander et al, 2010).

Conclusion

Animal models have provided insight into the neural circuits, brain areas and molecular mechanisms that underlie the addictive process and factors governing withdrawal and relapse. Addictive drugs stimulate dopamine release from mesolimbic terminals in the nucleus accumbens and cause a rapid and persistent potentiation of glutamate stimulation of VTA dopamine neurons. The transition to addiction, which defines the shift from occasional controlled drug use to compulsive drug-taking, is associated with gene transcription and persistent impairment of synaptic plasticity in the nucleus accumbens, suggesting that the transition to drug addiction may be mediated by an inability to engage active processes to allow control of drug intake. Drugs of abuse produce pathological overstimulation of reward circuits in the brain, causing enduring molecular changes in target areas of the mesocorticolimbic dopaminergic system. Excessive induction of ΔFosB, resulting from chronic exposure to substances of abuse, leads to excessive sensitisation of the nucleus accumbens circuitry and pathological compulsive drug-seeking and drug-taking behaviour associated with addiction (Nestler, 2008). *In vivo* measurement of ΔFosB levels in the nucleus accumbens of addicted individuals, using radioactively labelled probes and positron emission tomography (PET) scanning techniques, could provide a measure of an individual's level of addiction, and drugs targeted at degradation of ΔFosB protein could possibly be of benefit in treating addiction (Nestler, 2008). In addition, microRNAs can inhibit gene transcription and limit the behavioural consequences of drug abuse, potentially offering a novel way of protecting humans from the consequences of drug addiction (Picciotto, 2010).

Acknowledgements

The authors wish to thank the University of Cape Town and the University of KwaZulu-Natal for support.

References

Abekawa T., Ohmori T., & Koyama, T. (1994). Effects of repeated administration of a high dose of methamphetamine on dopamine and glutamate release in rat striatum and nucleus accumbens. *Brain Research*, 643(1–2):276–81.

Acikgoz, O., Gonenc, S., Kayatekin, B.M., Uysal, N., Pekcetin, C., Semin, I. & Gure, A. (1998). Methamphetamine causes lipid peroxidation and an increase in superoxide dismutase activity in the rat striatum. *Brain Research*, 813(1):200–202.

Agarwal, R., & Shukla, G.S. (1999). Potential role of cerebral glutathione in the maintenance of blood-brain barrier integrity in rats. *Neurochemical Research*, 24(12):1507–14.

Akca, T., Canbaz, H., Tataroglu, C., Caglikulekci, M., Tamer, L., Colak, T., Kanik, A., Bilgin, O. & Aydin, S. (2005). The effect of N-acetylcysteine on pulmonary lipid peroxidation and tissue damage. *Journal of Surgical Research*, 129(1):38–45.

Anderson, S.M., Schmidt, H.D. & Pierce, R.C. (2006). Administration of the D2 dopamine receptor antagonist sulpiride into the shell, but not the core, of the nucleus accumbens attenuates cocaine priming-induced reinstatement of drug seeking. *Neuropsychopharmacology*, 31(7): 1452–61.

Baker, D.A., McFarland, K., Lake, R.W., Shen, H., Tang, X.C., Toda, S. & Kalivas, P.W. (2003). Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nature Neuroscience*, 6(7):743–49.

Battaglia, G., Fornai, F., Busceti, C.L., Aloisi, G., Cerrito, F., De Blasi, A., Melchiorri, D. & Nicoletti, F. (2002). Selective blockade of mGlu5 metabotropic glutamate receptors is protective against methamphetamine neurotoxicity. *The Journal of Neuroscience*, 22(6):2135–41.

Bechara, A. (2001). Neurobiology of decision-making: risk and reward. *Seminars in Clinical Neuropsychiatry*, 6(3):205–16.

Bergeron, R., Meyer, T.M., Coyle, J.T. & Greene, R.W. (1998). Modulation of N-methyl-D-aspartate receptor function by glycine transport. *Proceedings of the National Academy of Sciences*, 95(26):15730–34.

Bhupanapadu Sunkesula, S.R., Swain, U. & Babu, P.P. (2008). Cell death is associated with reduced base excision repair during chronic alcohol administration in adult rat brain. *Neurochemical Research*, 33(6):1117–28.

Bonci, A. & Borgland, S. (2009). Role of orexin/hypocretin and CRF in the formatin of drug-dependent synaptic plasticity in the mesolimbic system. *Neuropharmacology*, 56(Suppl. 1): 107–11.

Bousman, C.A., Glatt, S.J., Everall, I.P. & Tsuang, M.T. (2009). Genetic association studies of methamphetamine use disorders: a systematic review and synthesis. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 150B(8):1025–49.

Bowyer, J.F. & Ali, S. (2006). High doses of methamphetamine that cause disruption of the blood-brain barrier in limbic regions produce extensive neuronal degeneration in mouse hippocampus. *Synapse*, 60(7):521–32.

Bradberry, C.W., Barrett-Larimore, R.L., Jatlow, P. & Rubino, S.R. (2000). Impact of self-administered cocaine and cocaine cues on extracellular dopamine in mesolimbic and sensorimotor striatum in rhesus monkeys. *The Journal of Neuroscience*, 20(10):3874–83.

Brauer, L.H. & De Wit, H. (1997). High dose pimozide does not block amphetamine-induced euphoria in normal volunteers. *Pharmacology Biochemistry and Behavior*, 56(2):265–72.

Brodie, M.S. & Bunney, E.B. (1996). Serotonin potentiates dopamine inhibition of ventral tegmental area neurons in vitro. *Journal of Neurophysiology*, 76(3):2077–82.

Bush, G., Luu, P. & Posner, M.I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, 4(6):215–22.

Cameron, D.L. & Williams, J.T. (1994). Cocaine inhibits GABA release in the VTA through endogenous 5-HT. *The Journal of Neuroscience*, 14(11 Pt1):6763–67.

Carboni, E., Tanda, G.L., Frau, R. & Di Chiara, G. (1990). Blockade of the noradrenaline carrier increases extracellular dopamine concentrations in the prefrontal cortex: evidence that dopamine is taken up in vivo by noradrenergic terminals. *Journal of Neurochemistry*, 55(3):1067–70.

Cardinal, R.N., Parkinson, J.A., Hall, J. & Everitt, B.J. (2002). Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience and Biobehavioral Reviews*, 26(3):321–52.

Centonze, D., Picconi, B., Baurez, C., Borelli, E., Pisani, A., Bernardi, G. & Calabresi, P. (2002) Cocaine and amphetamine depress striatal GABAergic synaptoc transmission through D2 dopamine receptors. *Neuropsychopharmacology*, 26(2):164–75.

Chen, J., Kelz, M.B., Hope, B.T., Nakabeppu, Y. & Nestler, E.J. (1997). Chronic FRAs: stable variants of ΔFosB induced in brain by chronic treatments. *The Journal of Neuroscience*, 17(13):4933–41.

Chen, G., Shi, J., Hu, Z. & Hang, C. (2008). Inhibitory effect on cerebral inflammatory response following traumatic brain injury in rats: a potential neuroprotective mechanism of N-Acetylcysteine. *Mediators of Inflammation*, 2008:1–8.

Cornish, J.L., Duffy, P. & Kalivas, PW. (1999). A role for nucleus accumbens glutamate transmission in the relapse to cocaine-seeking behaviour. *Neuroscience*, 93(4):1359–67.

Cornish, J.L. & Kalivas, P.W. (2000). Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *The Journal of Neuroscience*, 20(15):1–5.

Cousins, M.S., Roberts, D.C. & De Wit, H. (2002). GABA(B) receptor agonists for the treatment of drug addiction: a review of recent findings. *Drug and Alcohol Dependence*, 65(3):209–20.

Dackis, C. & O'Brien, C. (2003). Glutamatergic agents for cocaine dependence. *Annals of the New York Academy of Sciences*, 1003:328–45.

De Boer, A.G. & Gaillard, P.J. (2006). Blood-brain barrier dysfunction and recovery. *Journal of Neural Transmission*, 113(4):455–62.

Demeule, M., Jodoin, J., Gingras, D. & Béliveau, R. (2000). P-glycoprotein is localized in caveolae in resistant cells and in brain capillaries. *FEBS Letters*, 466(2–3):219–24.

Dewey, S.L., Smith, G.S., Logan, J., Brodie, J.D., Yu, D.W., Ferrieri, R.A., King, P.T., MacGregor, R.R., Martin, T.P., Wolf, A.P., Volkow, N.D., Fowler, J.S. & Meller, E. (1992). GABAergic

inhibition of endogenous dopamine release measured in vivo with 11C-raclopride and positron emission tomography. *The Journal of Neuroscience*, 12(10):3773–80.

Di Chiara, G., Bassareo, V., Fenu, S., De Luca, M.A., Spina, L., Cadoni, C., Acquas, C., Carboni, E., Valentina, V. & Lecca, D. (2004). Dopamine and drug addiction: the nucleus accumbens shell connection. *Neuropharmacology* 47(Suppl. 1):227–41.

Di Ciano, P. & Everitt, B.J. (2001). Dissociable effects of antagonism of NMDA and AMPA/KA receptors in the nucleus accumbens core and shell on cocaine-seeking behaviour. *Neuropsychopharmacology*, 25(3):341–60.

Di Giovanni, G., Esposito, E. & Di Matteo, V. (2010). Role of serotonin in central dopamine dysfunction. *CNS Neuroscience & Therapeutics*, 16(3):179–94.

Di Mascio, M., Di Giovanni, G., Di Matteo, V., Prisco, E. & Esposito E. (1998). Selective serotonin reuptake inhibitors reduce the spontaneous activity of dopaminergic neurons in the ventral tegmental area. *Brain Research Bulletin*, 46(6):547–54.

Di Matteo, V., De Blasi, A., Di Giulio, C. & Esposito, E. (2001). Role of 5-HT(2C) receptors in the control of central dopamine function. *Trends in Pharmacological Sciences*, 22(5):229–32.

Di Matteo, V., Di Giovanni, G., Di Mascio, M. & Esposito, E. (2000). Biochemical and electrophysiological evidence that RO 600175 inhibits mesolimbic dopaminergic function through serotonin (2C) receptors. *Brain Research*, 865(1):85–90.

Drevets, W.C., Gautier, C., Price, J.C., Kupfer, D.J., Kinahan, P.E., Grace, A.A., Price, J.L. & Mathis, C.A. (2001). Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biological Psychiatry*, 49(2):81–96.

Drevets, W.C., Price, J.C., Kupfer, D.J., Kinahan, P.E., Lopresti, B., Holt, D. & Mathis, C. (1999). PET measures of amphetamine-induced dopamine release in ventral versus dorsal striatum. *Neuropsychopharmacology*, 21(6):694–709.

Eberle-Wang, K., Mikeladze, Z., Uryu, K. & Chesselet, M.F. (1997). Pattern of expression of the serotonin2C receptor messenger RNA in the basal ganglia of adult rats. *The Journal of Comparative Neurology*, 384(2):233–47.

Edwards, S. & Koob, G.F. (2010). Neurobiology of dysregulated motivational systems in drug addiction. *Future Neurology*, 5(3):393–401.

Eshleman, A.J., Carmolli, M., Cumbay, M., Martens, C.R., Neve, K.A. & Janowsky, A. (1999). Characteristics of drug interactions with recombinant biogenic amine transporters expressed in the same cell type. *Journal of Pharmacology and Experimental Therapeutics*, 289(2):877–85.

Everitt, B.J., Cardinal, R.N., Parkinson, J.A. & Robbins, T.W. (2003). Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. *Annals of the New York Academy of Sciences*, 985:233–50.

Faure, J.J., Hattingh, S.M., Stein, D.J. & Daniels, W.M. (2009). Proteomic analysis reveals differentially expressed proteins in the rat frontal cortex after methamphetamine treatment. *Metabolic Brain Disease*, 24(4):685–700.

Frantz, K.J., Hansson, K.J., Stouffer, D.G. & Parsons, L.H. (2002). 5-HT_6 receptor antagonism potentiates the behavioral and neurochemical effects of amphetamine but not cocaine. *Neuropharmacology*, 42(2):170–80.

Friedman, N.P. & Miyake, A. (2004). The relations among inhibition and interference control functions: a latent-variable analysis. *Journal of Experimental Psychology: General*, 133(1):101–35.

Fuller, R.W., Hemrick-Luecke, S.K. & Ornstein, P.L. (1992). Protection against amphetamine-induced neurotoxicity toward striatal dopamine neurons in rodents by LY274614, an excitatory amino acid antagonist. *Neuropharmacology*, 31(10):1027–32.

Fumagalli, F., Gainetdinov, R.R., Wang, Y.M., Valenzano, K.J., Miller, G.W. & Caron, M.G. (1999). Increased methamphetamine neurotoxicity in heterozygous vesicular monoamine transporter 2 knock-out mice. *The Journal of Neuroscience*, 19(7):2424–31.

Gerasimov, M.R., Ashby, C.R., Jr, Gardner, E.L., Mills, M.J., Brodie, J.D. & Dewey, S.L. (1999). Gamma-Vinyl GABA inhibits methamphetamine, heroin, or ethanol-induced increases in nucleus accumbens dopamine. *Synapse*, 34(1):11–19.

Gluck, M.R., Moy, L.Y., Jayatilleke, E., Hogan, K.A., Manzino, L. & Sonsalla, P.K. (2001). Parallel increases in lipid and protein oxidative markers in several mouse brain regions after methamphetamine treatment. *Journal of Neurochemistry*, 79(1):152–60.

Good, C.H. & Lupica, C.R. (2010). Afferent-specific AMPA receptor subunit composition and regulation of synaptic plasticity in midbrain dopamine neurons by abused drugs. *Journal of Neuroscience*, 30(23):7900–909.

Grenhoff, J., Nisell, M., Ferre, S., Aston-Jones, G. & Svensson, T.H. (1993). Noradrenergic modulation of midbrain dopamine cell firing elicited by stimulation of the locus coeruleus in the rat. *Journal of Neural Transmission, General Section*, 93(1):11–25.

Gunasekar, P.G., Kanthasamy, A.G., Borowitz, J.L. & Isom, G.E. (1995). NMDA receptor activation produces concurrent generation of nitric oxide and reactive oxygen species: implication for cell death. *Journal of Neurochemistry*, 65(5):2016–21.

Harold, C., Wallace, T., Friedman, R., Gudelsky, G. & Yamamoto, B. (2000). Methamphetamine selectively alters brain glutathione. *European Journal of Pharmacology*, 400(1):99–102.

Hiroi, N., Brown, J., Haile, C., Ye, H., Greenberg, M.E. & Nestler, E.J. (1997). FosB mutant mice: loss of chronic cocaine induction of Fos-related proteins and heightened sensitivity to cocaine's psychomotor and rewarding effects. *Proceedings of the National Academy of Science*, 94(19):10397–402.

Hirsch-Ernst, K.I. & Kietzmann, T. (2000). Physiological oxygen tensions modulate expression of the mdr1b multidrug-resistance gene in primary rat hepatocyte cultures. *Biochemistry Journal*, 350(Pt 2):443–51.

Hollander, J.A., Im, H.I., Amelio, A.L., Kocerha, J., Bali, P., Lu, Q., Willoughby, D., Wahlestedt, C., Conkright, M.D. & Kenny, P.J. (2010). Striatal microRNA controls cocaine intake through CREB signalling. *Nature*, 466(7303):197–202.

Hong, H., Lu, Y., Ji, Z.N. & Liu, G.Q. (2006). Up-regulation of P-glycoprotein expression by glutathione depletion-induced oxidative stress in rat brain microvessel endothelial cells. *Journal of Neurochemistry*, 98(5):1465–73.

Hu, G., Duffy, P., Swanson, C., Ghasemzadeh, M.B. & Kalivas, P.W. (1999). The regulation of dopamine transmission by metabotropic glutamate receptors. *Journal of Pharmacology and Experimental Therapeutics*, 289(1):412–16.

Hyman, S.E. & Malenka, R.C. (2001). Addiction and the brain, the neurobiology of compulsion and its persistence. *Nature Reviews Neuroscience*, 2(10):695–703.

Ito, R., Dalley, J.W., Robbins, T.W. & Everitt, B.J. (2002). Dopamine release in the dorsal striatum during cocaine-seeking behaviour under the control of a drug-associated cue. *The Journal of Neuroscience*, 22(14):6247–53.

Iversen, L. (2006). Neurotransmitter transporters and their impact on the development of psychopharmacology. *British Journal of Pharmacology*, 147(Suppl. 1):S82–S88.

Iwazaki, T., McGregor, I.S. & Matsumoto, I. (2006). Protein expression profile in the striatum of acute methamphetamine-treated rats. *Brain Research*, 1097(1):19–25.

Jay, T.M. (2003). Dopamine: a potential substrate for synaptic plasticity and memory mechanisms. *Progress in Neurobiology*, 69(6):375–90.

Jentsch, J.D. & Taylor, J.R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behaviour by reward-related stimuli. *Psychopharmacology (Berl)*, 146(4):373–90.

Jin, X., Semenova, S., Yang, L., Ardecky, R., Sheffler, D.J., Dahl, R., Conn, P.J., Cosford, N.D.P. & Markou, A. (2010). The mGluR2 positive allosteric modulator BINA decreases cocaine self-administration and cue-induced cocaine-seeking and counteracts cocaine-induced enhancement of brain reward function in rats. *Neuropsychopharmacology*, 35(10):2021–36.

Johnson, J.W. & Ascher, P. (1987). Glycine potentiates the NMDA response in cultures mouse brain neurons. *Nature*, 325(6104):529–31.

Kalivas, P.W. & Duffy, P. (1995). D1 receptors modulate glutamate transmission in the ventral tegmental area. *The Journal of Neuroscience*, 15(7 Pt 2):5379–88.

Kalivas, P.W., McFarland, K., Bowers, S., Szumlinski, K., Xi, Z.X. & Baker, D. (2003). Glutamate transmission and addiction to cocaine. *Annals of the New York Academy of Sciences*, 1003:169–75.

Kalivas, P.W. & Volkow, N.D. (2005). The neural basis of addiction: a pathology of motivation and choice. *American Journal of Psychiatry*, 162(8):1403–13.

Kalivas, P.W., Volkow, N. & Seamans, J. (2005). Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. *Neuron*, 45(5):647–50.

Kampman, K.M., Pettinati, H., Lynch, K.G., Dackis, C., Sparkman, T., Weigley, C. & O'Brien, C.P. (2004). A pilot trial of topiramate for the treatment of cocaine dependence. *Drug and Alcohol Dependence*, 75(3):233–40.

Karler, R., Calder, L.D., Thai, D.K. & Bedingfield, J.B. (1998). The role of dopamine and GABA in the frontal cortex of mice in modulating a motor-stimulant effect of amphetamine and cocaine. *Pharmacology Biochemistry and Behavior*, 60(1):237–44.

Kasanetz, F., Deroche-Gamonet, V., Berson, N., Balado, E., Lafourcade, M., Manzoni, O. & Piazza, P.V. (2010). Transition to addiction is associated with a persistent impairment in synaptic plasticity. *Science*, 328(5986):1709–12.

Kelley, A.E. (2004). Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. *Neuroscience and Biobehavioral Reviews*, 27(8):765–76.

Kelley, A.E. & Berridge, K.C. (2002). The neuroscience of natural rewards: relevance to addictive drugs. *The Journal of Neuroscience*, 22(9):3306–11.

Kelz, M.B., Chen, J., Carlezon, W.A., Jr, Whisler, K., Gilden, L., Beckmann, A.M., Steffen, C., Zhang, Y.J., Marotti, L., Self, D.W., Tkatch, T., Baranauskas, G., Surmeier, D.J,. Neve, R.L., Duman, R.S., Picciotto, M.R. & Nestler, E.J. (1999). Expression of the transcription factor ΔFosB in the brain controls sensitivity to cocaine. *Nature*, 401(6750):272–76.

Keys, A.S., Mark, G.P., Emre, N. &Meshul, C.K. (1998). Reduced glutamate immunolabeling in the nucleus accumbens following extended withdrawal from self-administered cocaine. *Synapse*, 30(4):393–401.

Kinney, G.G., Sur, C., Burno, M., Mallorga, P.J., Williams, J.B., Figueroa, D.J., Wittmann, M., Lemaire, W. & Conn, P.J. (2003). The glycine transporter type 1 inhibitor N-[3-(4'-fluorophenyl)-3-(4'-phenylphenoxy)propyl]sarcosine potentiates NMDA receptor-mediated responses in vivo and produces an antipsychotic profile in rodent behavior. *The Journal of Neuroscience*, 23(20):7586–91.

Kita, H. & Kitai, S.T. (1988). Glutamate decarboxylase immunoreactive neurons in rat neostriatum: their morphological types and populations. *Brain Research*, 447(2):346–52.

Kita, T., Wagner, G.C., Philbert, M.A., King, L.A. & Lowndes, H.E. (1995). Effects of pargyline and pyrogallol on the methamphetamine-induced dopamine depletion. *Molecular and Chemical Neuropathology*, 24(1):31–41.

Koob, G.F. (2009). New dimensions in human laboratory models of addiction. *Addiction Biology*, 14(1):1–8.

Koob, G.F. & Volkow, N.D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, 35(1):217–38.

Krasnova, I.N. & Cadet, J.L. (2009). Methamphetamine toxicity and messengers of death. *Brain Research Reviews*, 60(2):379–407.

Kushner, S.A., Dewey, S.L. & Kornetsky, C. (1999). The irreversible gamma-vinyl-GABA blocks cocaine self-administration in rats. *Journal of Pharmacology and Experimental Therapeutics*, 290(2):797–802.

Larson, E.R. & Ariano, M.A. (1995). D3 and D2 dopamine receptors: visualization of cellular expression patterns in motor and limbic structures. *Synapse*, 20(4):325–37.

Lategan, A.J., Marien, M.R. & Colpaert, F.C. (1990). Effects of locus coeruleus lesions on the release of endogenous dopamine in the rat nucleus accumbens and caudate nucleus as determined by intracerebral microdialysis. *Brain Research*, 523(1):134–38.

Laube, B., Hirai, H., Sturgess, M., Betz, H. & Kuhse, J. (1997). Molecular determinants of agonist discrimination by NMDA receptor subunits: Analysis of the glutamate binding site on the NR2B subunit. *Neuron*, 18(3):493–503.

LaVoie, M.J. & Hastings, T.G. (1999). Dopamine quinone formation and protein modification associated with the striatal neurotoxicity of methamphetamine: evidence against a role for extracellular dopamine. *The Journal of Neuroscience*, 19(4):1484–91.

Li, X., Li, J., Gardner, E.L. & Xi, Z.X. (2010). Activation of mGluR7s inhibits cocaine-induced reinstatement of drug-seeking behavior by a nucleus accumbens glutamate-mGluR2/3 mechanism in rats. *Journal of Neurochemistry*, 114(5):1368–80.

Li, X., Wang, H., Qiu, P. & Luo, H. (2008). Proteomic profiling of proteins associated with methamphetamine-induced neurotoxicity in different regions of rat brain. *Neurochemistry International*, 52(1–2):256–64.

Lu, L., Koya, E., Zhai, H., Hope, B.T. & Shaham, Y. (2006). Role of ERK in cocaine addiction. *Trends in Neurosciences*, 29(12):695–703.

Mahajan, S., Aslinkeel, R., Sykes, D.E., Reynolds, J.L., Bindukumar, B., Adal, A., Qi, M., Toh, J., Xu, G., Prasad, P.N. & Schwartz, S.A. (2008). Methamphetamine alters

blood brain barrier permeability via the modulation of tight junction expression: implication for HIV-1 neuropathogenesis in the context of drug abuse. *Brain Research*, 1203:133–48.

Mark, K.A., Soghomonian, J.J. & Yamamoto, B.K. (2004). High-dose methamphetamine acutely activates the striatonigral pathway to increase striatal glutamate and mediate long-term dopamine toxicity. *The Journal of Neuroscience*, 24(50):11449–456.

McClure, S.M., Daw, N.D. & Montague, P.R. (2003). A computational substrate for incentive salience. *Trends in Neuroscience*, 26(8):423–28.

McDonald, R.J. & White, N.M. (1993). A triple dissociation of memory systems: hippocampus, amygdala and dorsal striatum. *Behavioral Neuroscience*, 107(1):3–22.

McFarland, K., Davidge, S.B., Lapish, C.C. & Kalivas, P.W. (2004). Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. *The Journal of Neuroscience*, 24(7):1551–60.

McFarland, K., Lapish, C.C. & Kalivas, P.W. (2003). Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *The Journal of Neuroscience*, 23(8):3531–37.

McGeehan, A.J. & Olive, M.F. (2003). The mGluR5 antagonist MPEP reduces the conditioned rewarding effects of cocaine but not other drugs of abuse. *Synapse*, 47(3):240–42.

Miyazaki, I., Asanuma, M., Diaz-Corrales, F.J., Fukuda, M., Kitaichi, K., Miyoshi, K. & Ogawa, N. (2006). Methamphetamine-induced dopaminergic neurotoxicity is regulated by quinone-formation-related molecules. *The FASEB Journal*, 20(3):571–73.

Napier, T.C. & Mitrovic, I. (1999). Opioid modulation of ventral pallidal inputs. *Annals of the New York Academy of Sciences*, 877:176–201.

Nestler, E.J. (2004). Molecular mechanisms of drug addiction. *Neuropharmacology* 47 (Suppl. 1):24–32.

Nestler, E.J. (2008). Transcriptional mechanisms of addiction: role of DeltaFosB. *Philosophical Transactions of the Royal Society. B, Biological Sciences*, 363(1507):3245–55.

Nestler, E.J., Barrot, M. & Self, D.W. (2001). DeltaFosB: a sustained molecular switch for addiction. *Proceedings of the National Academy of Science*, 98(20):11042–11046.

Nestler, E.J., Kelz, M.B. & Chen, J. (1999). DeltaFosB: a molecular mediator of long-term neural and behavioral plasticity. *Brain Research*, 835(1):10–17.

Niehaus, J.L., Murali, M. & Kauer, J.A. (2010). Drugs of abuse and stress impair LTP at inhibitory synapses in the ventral tegmental area. *European Journal of Neuroscience*, 32(1):108–117.

Parsons, L.H., Weiss, F. & Koob, G.F. (1998). Serotonin 1B receptor stimulation enhances cocaine reinforcement. *The Journal of Neuroscience*, 18(23):10078–89.

Pascual, M., Boix, J., Felipo, V. & Guerri, C. (2009). Repeated alcohol administration during adolescence causes changes in the mesolimbic dopaminergic and glutamatergic systems and promotes alcohol intake in the adult rat. *Journal of Neurochemistry*, 108(4):920–31.

Phelix, C.F. & Broderick, P.A. (1995). Light microscopic immunocytochemical evidence of converging serotonin and dopamine terminals in ventrolateral nucleus accumbens. *Brain Research Bulletin*, 37(1):37–40.

Picciotto, M.R. (2010). MicroRNA knocks down cocaine. *Nature*, 466(7303):194–95.

Pierce, R.C., Bell, K., Duffy, P. & Kalivas, P.W. (1996). Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. *The Journal of Neuroscience*, 16(4):1550–60.

Pierce, R.C. & Kumaresan, V. (2006). The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? *Neuroscience & Biobehavioral Reviews*, 30(2):215–38.

Plateel, M., Dehouck, M.P., Torpeir, G., Cecchelli, R. & Teissier, E. (1995). Hypoxia increases the susceptability to oxidant stress and the permeability of the blood-brain barrier endothelial cell monolayer. *Journal of Neurochemistry*, 65(5):2138–45.

Plüddemann, A., Dada, S., Williams, Y., Bhana, A., Pereira, T., Carelsen, A., Kitleli, N., Gerber, W., Rosslee, C., Parry, C.D.H. & Fourie, D. *Monitoring Alcohol and Drug Abuse Trends in South Africa.* Proceedings of SACENDU Report Back Meetings, May 2009: July–December 2008 (Phase 25). Parow: Medical Research Council, 2009.

Porras, G., Di Matteo, V., Fracasso, C., Lucas, G., De Deurwaerdère, P., Caccia, S., Esposito, E. & Spampinato, U. (2002). 5-HT_{2A} and 5-$HT_{2C/2B}$ receptor subtypes modulate dopamine release induced in vivo by amphetamine and morphine in both the rat nucleus accumbens and striatum. *Neuropsychopharmacology*, 26(3):311–24.

Potashkin, J.A. & Meredith, G.E. (2006). The role of oxidative stress in the dysregulation of gene expression and protein metabolism in neurodegenerative disease. *Antioxidants and Redox Signaling*, 8(1–2):144–51.

Pulvirenti, L., Balducci, C. & Koob, G.F. (1997). Dextromethorphan reduces intravenous cocaine self-administration in the rat. *European Journal of Pharmacology*, 321(3):279–83.

Qiang, M., Denny, A.D. & Ticku, M.K. (2007). Chronic intermittent ethanol treatment selectively alters N-methyl-D-aspartate receptor subunit surface expression in cultured cortical neurons. *Molecular Pharmacology*, 72(1):95–102.

Qiang, M. & Ticku, M.K. (2005). Role of AP-1 in ethanol-induced N-methyl-D-aspartate receptor 2B subunit gene up-regulation in mouse cortical neurons. *Journal of Neurochemistry*, 95(5):1332–41.

Reid, M.S., Hsu, K., Jr & Berger, S.P. (1997). Cocaine and amphetamine preferentially stimulate glutamate release in the limbic system: studies on the involvement of dopamine. *Synapse*, 27(2):95–105.

Reith, M.E., Li, M.Y. & Yan, Q.S. (1997). Extracellular dopamine, norepinephrine, and serotonin in the ventral tegmental area and nucleus accumbens of freely moving rats during intracerebral dialysis following systemic administration of cocaine and other uptake blockers. *Psychopharmacology*, 134(3):309–17.

Robinson, T.E. & Berridge, K.C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research Brain Research Reviews*, 18(3):247–91.

Rolls, E.T. (2000). The orbitofrontal cortex and reward. *Cerebral Cortex*, 10(3):284–94.

Rothman, R.B., Baumann, M.H., Dersch, C.M., Romero, D.V., Rice, K.C., Carroll, F.I. & Partilla J.S. (2001). Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*, 39(1):32–41.

Royall, D.R., Lauterbach, E.C., Cummings, J.L., Reeve, A., Rummans, T.A., Kaufer, D.I., LaFrance, W.C., Jr & Coffey, C.E. (2002). Executive control function: a review of its

promise and challenges for clinical research. A report from the Committee on Research of the American Neuropsychiatric Association. *Journal of Neuropsychiatry and Clinical Neurosciences*, 14(4):377–405.

Ruat, M., Traiffort, E., Arrang, J.M., Tardivel-Lacombe, J., Diaz, J., Leurs, R. & Schwartz, J.C. (1993). A novel rat serotonin (5-HT6) receptor: molecular cloning, localization and stimulation of cAMP accumulation. *Biochemistry and Biophysical Research Communications*, 193(1):268–76.

Russell, V.A. (2000). The nucleus accumbens motor-limbic interface of the spontaneously hypertensive rat (SHR) as studied in-vitro by the superfusion technique. *Neuroscience & Biobehavioral Reviews*, 24(1):133–36.

Russell, V.A., Sagvolden, T. & Johansen, E.B. (2005). Animal models of attention-deficit hyperactivity disorder. *Behavioral and Brain Functions*, 1:9.

Sagvolden, T., Russell, V.A., Aase, H., Johansen, E.B. & Farshbaf, M. (2005). Rodent models of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 57(11):1239–47.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, 80(1):1–27.

See, R.E., Kruzich, P.J. & Grimm, J.W. (2001). Dopamine, but not glutamate, receptor blockade in the basolateral amygdala attenuates conditioned reward in a rat model of relapse to cocaine-seeking behavior. *Psychopharmacology (Berl)*, 154(3):301–10.

Sellings, L.H. & Clarke, P.B. (2003). Segregation of amphetamine reward and locomotor stimulation between nucleus accumbens medial shell and core. *The Journal of Neuroscience*, 23(15):6295–303.

Steffensen, S.C., Svingos, A.L., Pickel, V.M. & Henriksen, S.J. (1998). Electrophysiological characterization of GABAergic neurons in the ventral tegmental area. *The Journal of Neuroscience*, 18(19):8003–15.

Stephens, D.N. & Duka, T. (2008). Cognitive and emotional consequences of binge drinking: role of amygdala and prefrontal cortex. *Philosophical Transactions of the Royal Society. B, Biological Sciences*, 363(1507):3169–79.

Sulzer, D., Sonders, M.S., Poulsen, N.W. & Galli, A. (2005). Mechanisms of neurotransmitter release by amphetamines: a review. *Progress in Neurobiology*, 75(6):406–33.

Torres, G.E., Gainetdinov, R.R. & Caron, M.G. (2003). Plasma membrane monoamine transporters: structure, regulation and function. *Nature Reviews Neuroscience*, 4(1):13–25.

Valjent, E., Pagès, C., Hervé, D., Girault, J.A. & Caboche, J. (2004). Addictive and non-addictive drugs induce distinct and specific patterns of ERK activation in mouse brain. *European Journal of Neuroscience*, 19(7):1826–36.

Vanderschuren, L.J. & Everitt, B.J. (2004). Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science*, 305(5686):1017–19.

Ventura, R., Cabib, S., Alcaro, A., Orsini, C. & Puglisi-Allegra, S. (2003). Norepinephrine in the prefrontal cortex is critical for amphetamine-induced reward and mesoaccumbens dopamine release. *The Journal of Neuroscience*, 23(5):1879–85.

Vergo, S., Johansen, J.L., Leist, M. & Lotharius, J. (2007). Vesicular monoamine transporter 2 regulates the sensitivity of rat dopaminergic neurons to disturbed cytosolic dopamine levels. *Brain Research*, 1185:18–32.

Vialou, V., Robison, A.J., LaPlant, Q.C., Covington, H.E., Dietz, D.M., Ohnishi, Y.N., Mouzon, E., Rush, A.J., Watts, E.L., Wallace, D.L., Iñiguez, S.D., Ohnishi, Y.H., Steiner, M.A., Warren, B.L., Krishnan, V., Bolaños, C.A., Neve, R.L., Ghose, S., Berton, O., Taminga, C.A. & Nestler, E.J. (2010). ΔFosB in brain reward circuits mediates resilience to stress and antidepressant responses. *Nature Neuroscience*, 13(6):745–52.

Vilpoux, C., Warnault, V., Pierrefiche, O., Daoust, M. & Naassila, M. (2009). Ethanol-sensitive brain regions in rat and mouse: a cartographic review, using immediate early gene expression. *Alcoholism: Clinical and Experimental Research*, 33(6):945–69.

Vogt, B.A., Finch, D.M. & Olson, C.R. (1992). Functional heterogeneity in cingulate cortex; the anterior executive and posterior evaluative regions. *Cerebral Cortex*, 2(6):435–43.

Volkow, N.D., Fowler, J.S. & Wang, G.J. (2003). The addicted human brain: insights from imaging studies. *Journal of Clinical Investigations*, 111(10):1444–51.

Volkow, N.D. & Li, T.K. (2005). The neuroscience of addiction. *Nature Neuroscience*, 8(11):1429–30.

Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Gatley, S.J., Wong, C., Hitzemann, R. & Pappas, N.R. (1999). Reinforcing effects of psychostimulants in humans are associated with increase in brain dopamine and occupancy of D2 receptors. *Journal of Pharmacology and Experimental Therapeutics*, 291(1):409–15.

Vorel, S.R., Liu, X., Hayes, R.J., Spector, J.A. & Gardner, E.L. (2001). Relapse to cocaine-seeking after hippocampal theta burst stimulation. *Science*, 292(5519):1175–78.

Wang, J., Carnicella, S., Phamluong, K., Jeanblanc, J., Ronesi, J.A., Chaudhri, N., Janak, P.H., Lovinger, D.M. & Ron, D. (2007). Ethanol induces long-term facilitation of NR2B-NMDA receptor activity in the dorsal striatum: implications for alcohol drinking behavior. *Journal of Neurochemistry*, 27(13):3593–602.

Waraczynski, M.A. (2006). The central extended amygdala network as a proposed circuit underlying reward valuation. *Neuroscience & Biobehavioral Reviews*, 30(4):472–96.

Weihe, E. & Eiden, L.E. (2000). Chemical neuroanatomy of the vesicular amine transporters. *The FASEB Journal*, 14(15):2435–49.

Whitelaw, R.B., Markou, A., Robbins, T.W. & Everitt, B.J. (1996). Excitotoxic lesions of the basolateral amygdala impair the acquisition of cocaine-seeking behavior under a second-order schedule of reinforcement. *Psychopharmacology (Berl)*, 127(3):213–24.

Wilhelm, C.J., Johnson, R.A., Eshleman, A.J. & Janowsky, A. (2006). Hydrogen ion concentration differentiates effects of methamphetamine and dopamine on transporter-mediated efflux. *Journal of Neurochemistry*, 96(4):1149–59.

Wilhelm, C.J., Johnson, R.A., Lysko, P.G., Eshleman, A.J. & Janowsky, A. (2004). Effects of methamphetamine and lobeline on vesicular monoamine and dopamine transporter-mediated dopamine release in a cotransfected model system. *Journal of Pharmacology and Experimental Therapeutics*, 310(3):1142–51.

Willner, P. (1986). Validation criteria for animal models of human disorders: learned helplessness as a paradigm case. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 10(6):677–90.

Wise, R.A. (2002). Brain reward circuitry: insights from unsensed incentives. *Neuron*, 36(2):229–40.

Wise, R.A. & Rompre, P.P. (1989). Brain dopamine and reward. *Annual Review of Psychology*, 40:191–225.

Wolf, M.E. (1998). The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants. *Progress in Neurobiology*, 54(6):679–720.

Wu, J., Hong, H., Ji, H., Wang, Y.Y., Wang, Y., Li, Y.Q., Li, W.G., Long, Y. & Xia,Y.Z. (2009). Glutathione depletion upregulates P-glycoprotein expression at the blood-brain barrier in rats. *Journal of Pharmacy and Pharmacology*, 61(6):819–24.

Xi, Z.X., Ramamoorthy, S., Baker, D.A., Shen, H., Samuvel, D.J. & Kalivas, P.W. (2002). Modulation of group II metabotropic glutamate receptor signaling by chronic cocaine. *Journal of Pharmacology and Experimental Therapeutics*, 303(2):608–15.

Yamamoto, B.K. & Zhu, W. (1998). The effects of methamphetamine on the production of free radicals and oxidative stress. *Journal of Pharmacology and Experimental Therapeutics*, 287(1):107–14.

Zahniser, N.R. & Sorkin, A. (2004). Rapid regulation of the dopamine transporter: role in stimulant addiction? *Neuropharmacology*, 47(Suppl. 1):80–91.

Zhai, H., Li, Y., Wang, X. & Lu, L. (2007). Drug-induced alterations in the extracellular signal-regulated kinase (ERK) signalling pathway: implications for reinforcement and reinstatement. *Cell and Molecular Neurobiology*, 28(2):157–72.

Zhang, X., Banerjee, A., Banks, W.A. & Ercal, N. (2009). N-Acetylcysteine amide protects against methamphetamine-induced oxidative stress and neurotoxicity in immortalized human brain endothelial cells. *Brain Research*, 1275:87–95.

Ziemann, C., Bürkle, A., Kahl, G.F. & Hirsch-Ernst, K.I. (1999). Reactive oxygen species participate in mdr1b mRNA and P-glycoprotein overexpression in primary rat hepatocyte cultures. *Carcinogenesis*, 20(3):407–14.

Intervention and Policy

13 Youth and substances

Neo K. Morojele, Eileen Rich, Alan J. Flisher and Bronwyn Myers

Introduction

The use and abuse of legal and illegal substances among adolescents and youth is of major concern in South Africa. Not only have there been increases in the proportion of young people engaged in the use of certain drugs (as shown below), but so have there been increases in the range of illegal drugs available to young people in the country since 1994. The increase in availability is due to the large amounts of drugs crossing South Africa's borders, as well as the increased local production of a range of drugs – including cannabis, methamphetamine, crystal methamphetamine (tik) and methcatinone (cat) – for both domestic and international consumption (UNODC, 2009).

According to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), of the American Psychiatric Association (1994), and the *International Classification of Diseases*, 10th edition (ICD-10), of the World Health Organization (WHO) there are two major types of substance use-related problems (see also Chapter 2). These include the use of substances that lead to social, physical or psychological harm (substance abuse or harmful use) on the one hand, and substance dependence, on the other hand. Although these classification systems were developed based on adult samples, they are used for diagnosing substance use-related problems among adolescents and youth, and have some limitations in this regard (eg, Fulkerson et al, 1999; Martin & Winters, 1998). In general, only a minority of young people who use substances can be classified as substance-dependent. A larger proportion of young people abuse or engage in harmful use of alcohol and other drugs (than are dependent users), while a further group engage in experimental or recreational use, that is, use without any notable current problems. For example, a household survey of over 4 000 adolescents aged 11–17 years in a metropolitan area (Houston, Texas), revealed prevalence rates of any substance use disorder of 5.27%; of alcohol abuse or dependence of 2.92%; of marijuana abuse or dependence of 3.38%; and of other substances abuse or dependence of 0.90% (Roberts et al, 2007). One South African study has estimated rates of substance abuse and dependence for adults to be as follows: 7.0% for alcohol abuse; 15.0% for alcohol dependence; 1.0% for drug abuse; and 3.0% for drug dependence (Kleintjies et al, 2006), but estimates for adolescents are lacking.

For the present purpose, our focus is limited to the use of psychoactive drugs among adolescents and young people in South Africa, and we use World Health Organization (WHO) definitions of adolescents (ie, those aged 10–19 years) and youth (those aged from 15 to 24 years). We consider both legal (primarily alcohol) and illegal drugs (mainly Mandrax, cannabis, methamphetamine, heroin and cocaine), but make little reference to

over-the-counter and prescription medications, although these categories of drugs are also used (primarily by adults) and are also a source of problems in South Africa (Myers, Siegfried & Parry, 2003).

Nature and extent of substance use by adolescents and youth

The primary sources of information on substance use among young people in South Africa are (1) a sentinel surveillance network on drug use, known as the South African Community Epidemiology Network on Drug Use (SACENDU; Parry et al, 2004b); (2) school-based surveys; and (3) household surveys. SACENDU has been tracking drug use trends, primarily from treatment centres, since 1996. This network provides an indication of trends in treatment admissions. SACENDU has shown regional variations in drug use trends. For example, for young patients in treatment centres in Gauteng during the second half of 2009, the most common primary substances of abuse were cannabis (57%), alcohol (14%) and heroin (6%). For Durban, they were cannabis (48%), heroin (22%) and alcohol (20%). For those in Cape Town, the most common substances were cannabis (43%), methamphetamine (39%) and alcohol (only 3%). The reasons for the different choices of drugs per region may be a reflection of availability.

SACENDU has also shown increases in the proportion of young people (under 20 years) in treatment for drug use over time, although more recently there seems to be some evidence of a reduction in these proportions. As shown in Figure 13.1, in 1998 (two years after the network was established) young people under 20 years comprised between 6% and 13% of the total population of patients in treatment. Ten years later, they made up approximately 20% of the total patient population. This increase is difficult to interpret, and may be attributable to numerous factors, including an increase in adolescents' demand for treatment, an increase in the accessibility of treatment for young people, a decrease in the demand for treatment among adults and/or changes in the admissions policies of the centres involved in the network.

There have been two school-based studies with nationally representative samples in which rates of substance use among school students were reported (see Table 14.1). These were part of the Youth Risk Behaviour Survey (YRBS) for 2002 (Reddy et al, 2003) and 2008 (Reddy et al, 2010). The substances that had the highest reported rates of lifetime use in 2002 were alcohol (56.1% and 43.5% for males and females, respectively), tobacco (40.0% and 23.0%) and cannabis (20.2% and 7.0%). In 2008, they were the same substances; that is, alcohol (54.4% and 45.1% for males and females, respectively), tobacco (36.8% and 22.4%), and cannabis (17.9% and 7.6%). While students' rates of use of most drugs were relatively stable between 2002 and 2008, the increases in rates of past 30-day alcohol use and binge drinking for both males and females are cause for concern (see Table 13.1). Changes in the prevalence of use of other drugs were observed by Flisher et al (2006) in a study reporting secular trends in substance use among Grade 8 students in Cape Town between 1997 and 2004. They concluded that there were significant increases in the prevalence of past-month use of cigarettes for males (from 23.0% to 31.5%), and cannabis for both males (3.1% to 17.2%) and females (1.9% to 5.2%). Furthermore, while crystal methamphetamine (tik) was not used to any detectable extent by high school students in 2002, two reports

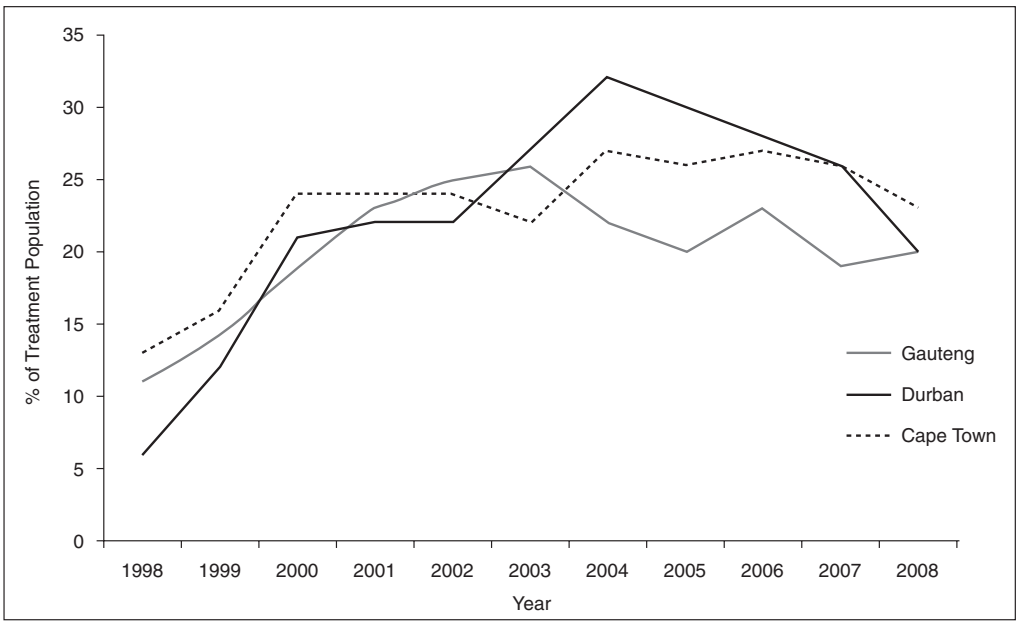

Figure 13.1: Proportion of treatment population under age 20 years in Gauteng, Durban and Cape Town between 1998 and 2008
Source: South African Community Epidemiology Network on Drug Use (SACENDU)

of school-based epidemiological studies in 2006 (Plüddemann et al, 2008; 2010) indicate a marked increase in the intervening period. The rates of crystal methamphetamine use by Grades 8 and 9 students in 2006 in one educational district in Cape Town (N = 1 561) were 8.8% for lifetime use; 4.7% for use in the past 12 months; and 2.8% in the past 30 days (Plüddemann et al, 2010). Rates of crystal methamphetamine use by Grade 9 students in the whole of Cape Town (N = 4 605) were 13.3% and 11.9% for males and females, respectively, for lifetime use; 62.8% and 44.8% for use in the past year among those who had ever used; and 61.0% and 59.7% for use in the past 30 days among those that had used in the past year (Plüddemann et al, 2008).

Very few household surveys of substance use among nationally representative samples of adolescents or youth have been conducted in South Africa. However, one useful source of nationally representative data among adolescents aged between 15 and 19 years is the 1998 and 2003 South Africa Demographic and Health Survey (SADHS) (1998 & 2003) of the Department of Health. Table 13.2 shows prevalence rates of lifetime, last 12 months and weekend 'risky drinking' or 'harmful and hazardous use' of adolescents based on data from 1998 and 2003, respectively. The 1998 survey defined 'risky drinking' as consumption of five or more drinks a day for men, and three or more drinks a day for women. The 2003 survey defined 'harmful drinking' as consumption of four to less than six drinks a day for men, and two to less than four drinks a day for women, and 'hazardous drinking' as consumption of six or more drinks a day for men and four or more drinks a day for women.

Table 13.1: Prevalence rates of use of selected substances among students in Grades 8–11, South Africa, 2002 (N = 10 699; Reddy et al, 2003), and 2008 (N = 10 270; Reddy et al, 2010)

		2002		2008	
	TIME	**BOYS (%)**	**GIRLS (%)**	**BOYS (%)**	**GIRLS (%)**
Alcohol	Ever	56.1	43.5	54.4	45.1
	30 days	38.5	26.4	40.5	29.5
	Binge drinking[1]	29.3	17.9	33.5	23.7
Tobacco	Ever	40.0	23.0	36.8	22.4
	30 days	29.0	14.9	26.4	15.8
Cannabis	Ever	20.2	7.0	17.9	7.6
	30 days	13.7	5.5	13.1	6.5
Inhalants	Ever	13.1	9.5	15.2	9.2
Mandrax	Ever	7.6	4.8	9.2	5.7
Cocaine	Ever	7.3	5.6	8.7	4.7
Heroin	Ever	11.8	11.3	7.4	5.0
'Club drugs'[2]	Ever	7.6	4.4	9.0	4.7
Over-the-counter[3]	Ever	16.4	14.8	12.8	11.3

[1] Defined as drinking five or more drinks of alcohol within a few hours on one or more days in the past month
[2] Including ecstasy, LSD, speed, magic mushrooms
[3] Refers to use of over-the-counter or prescription drugs to get high

In 1998, 25.3% of males and 15.0% of females reported ever having consumed alcohol. In 2003, these figures had increased markedly for males (to 31.9%) and slightly for females (to 17.2%). The proportion of males who had engaged in weekend risky drinking was 24.1% in 1998, and in 2003 9.3% had engaged in weekend hazardous or harmful drinking. For females, these figures were 27.3% in 1998 and 36.6% in 2003. In both years, there were higher levels of lifetime alcohol use (and in 2003 a higher rate of last 12 months alcohol use) among urban adolescents than among their non-urban counterparts. The non-urban adolescent males were more likely (32.2%) than their urban counterparts (20.5%) to engage in weekend risky drinking in 1998, although this pattern did not apply in 2003 to weekend hazardous and harmful drinking. Rates of hazardous and harmful drinking were also higher for the non-urban females (40.9%) than for the urban females (35.8%) in 2003. Adolescents in the Western Cape had among the highest levels of drinking behaviour (ie of lifetime and last 12 months), while those in Limpopo province tended to have among the lowest rates. Regarding weekend hazardous and harmful drinking in 2003, while males from the Western Cape continued to have the highest rates, females from four other provinces (the Northern Cape, KwaZulu-Natal, Mpumalanga and the Eastern Cape) all had higher rates than their counterparts in the Western Cape. Both surveys found that white adolescents had among

Table 13.2: Alcohol use (%) by adolescents (15–19 years), 1998 and 2003 South Africa Demographic and Health Survey

BACKGROUND CHARACTERISTICS	EVER DRANK ALCOHOL				DRANK IN LAST 12 MONTHS				WEEKEND RISKY DRINKING (1998)/ HAZARDOUS AND HARMFUL USE (2003)[1]			
	1998		2003		1998		2003		1998		2003	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Age												
15	12.4	8.2	22.8	14.5	-	-	20.8	12.6	*	*	3.2	40.1
16	21.1	10.2	24.7	18.0	-	-	22.7	13.8	17.2	*	3.1	25.6
17	23.5	16.8	24.3	21.4	-	-	17.0	17.2	29.8	*	8.9	37.6
18	28.6	18.9	36.3	14.4	-	-	31.0	10.4	32.7	*	8.4	49.5
19	43.8	21.9	50.0	17.7	-	-	45.1	14.8	22.2	*	16.1	32.8
Residence												
Urban	28.8	21.2	38.8	23.3	-	-	32.6	18.6	20.5	23.4	10.2	35.8
Non-urban	21.2	7.1	23.1	7.8	-	-	20.5	6.0	32.2	*	7.0	40.9
Province												
Western Cape	33.1	36.4	52.6	39.6	-	-	45.8	37.4	*	*	14.9	48.3
Eastern Cape	28.9	7.1	31.0	17.2	-	-	27.7	9.7	*	*	17.6	46.7
Northern Cape	28.4	18.1	33.2	41.3	-	-	31.8	34.2	*	*	41.9	25.9
Free State	20.0	11.3	24.3	17.2	-	-	21.6	12.6	*	*	0.0	41.0
KZN	21.7	8.7	16.1	7.4	-	-	11.7	3.4	*	*	17.3	51.2
North West	19.8	9.7	40.7	15.3	-	-	37.1	15.3	*	*	9.3	13.8
Gauteng	30.8	28.6	43.1	24.9	-	-	37.8	22.2	28.6	18.2	0.0	23.8
Mpumalanga	30.3	10.6	24.4	1.1	-	-	23.2	1.1	*	*	16.0	0.0
Limpopo	17.6	6.5	26.6	8.8	-	-	21.9	5.3	*	*	9.9	33.3
Pop. Group												
African	20.0	6.9	28.5	13.2	-	-	24.3	9.8	21.4	*	9.2	31.4
Afr. urban	20.0	8.8	33.1	18.4	-	-	27.7	13.6	12.7	*	10.7	31.4
Afr. non-urban	20.1	5.3	22.7	6.8	-	-	20.0	5.1	31.0	*	6.6	31.3
Coloured	32.9	33.8	56.1	42.3	-	-	50.1	37.8	*	*	5.7	66.6
White	70.1	65.1	64.8	32.2	-	-	64.8	32.2	21.7	25. 3	22.9	0.0
Indian/Asian	39.8	14.8	68.3	58.4	-	-	63.1	50.1	*	*	3.5	0.0
Total	25.3	15.0	31.9	17.2	-	-	27.7	13.7	24.1	27.3	9.3	36.6

Notes
* Too few cases to report data.
- Not assessed.
[1] 'Weekend risky drinking' among current drinkers in 1998 refers to consumption of five or more standard drinks per day for men, and three or more standard drinks per day for females over weekends. 'Hazardous and harmful drinking over weekends' refers to the consumption of four or more standard drinks per day for men (drinkers), and two or more standard drinks per day for women (drinkers) during weekends, over the seven days preceding the interview.
Source: Adapted from Department of Health (1998; 2003)

the highest levels of alcohol use. In 1998, 70.1% of white males and 65.1% of white females reported having ever drunk alcohol, as compared with 20.0% for African males and 6.9% for African females. In the 2003 survey, rates of lifetime use had fallen for white males (64%) and white females (32.2%), but had increased for black males (28.5%) and black females (13.2%).

Table 13.3 shows the proportions of male and female adolescents who had ever used tobacco products, and were current daily smokers. As expected, the proportion of lifetime smokers in both years increased sequentially from age 15 to 19. In addition, there were slight increases in rates of lifetime smoking between 1998 and 2003. In 1998, 11.1% of males and 4.4% of females were current daily smokers as compared to 14.2% of males and 5.1% of females in 2003. For both time points there were higher prevalence rates for tobacco use among adolescents from urban as opposed to non-urban areas. As with alcohol use, both male and female adolescents from the Western Cape had among the highest rates of lifetime use and current daily smoking. Low prevalence rates were evident for Limpopo, Mpumalanga and North West provinces for both males and females. White males had the highest rates of lifetime tobacco use in 1998 and 2003 (ie, 42.8% and 68.5%, respectively). White females had the highest lifetime use rates in 1998 (47.6%), but in 2003 coloured females had the highest rates among females (47.6%). Coloured males were most likely to be current daily smokers in both 1998 (25.9%) and in 2003 (47.4%). White females had the highest rate of current daily smoking in 1998, and coloured females had the highest rates in 2003. White females' smoking seems to be declining, while that of coloured females seems to be on the increase.

From the various findings of the studies on adolescent substance use described here, it is evident that certain demographic factors are consistently associated with levels of substance use. Specifically, males and older adolescents tend to have the highest rates of alcohol and other drug use, while black females in particular seem to be least likely to use any substances. These observations concur with findings of other studies of adolescent substance use in South Africa (eg, Flisher et al, 2003; Reddy et al, 2007).

Consequences

Substance use has both short- and long-term consequences for adolescents. The earlier an individual starts using drugs, the greater the risk of the development of substance use disorders, and other substance-related problems in later life (eg, Behrendt et al, 2009; York et al, 2004). The use of substances is directly and indirectly associated with mortality and morbidity among adolescents and youth. Death and disability (from overdoses) are the most severe consequences of the use and abuse of substances (Jernigan, 2001). However, social, psychological, physical and mental health problems are more common. We discuss problems within each of these areas in turn.

According to estimates of Tombourou and his colleagues (2007), using 2000 data, there were 3.6 million substance-related deaths among young people aged between 15 and 29 years globally. Approximately 86% of these substance-related deaths were attributable to hazardous alcohol use. For young males and females in developing countries, hazardous alcohol use was estimated to cause 6.3% and 1.1% of deaths, respectively; illicit drug use

Table 13.3: Tobacco use (%) by adolescents (15–19 years), 1998 and 2003 South African Demographic and Health Survey

BACKGROUND CHARACTERISTICS	EVER USED TOBACCO PRODUCTS				CURRENTLY SMOKING DAILY			
	1998		2003		1998		2003	
	Male	Female	Male	Female	Male	Female	Male	Female
Age								
15	6.3	5.4	7.0	7.9	2.8	1.6	1.0	5.2
16	15.0	5.4	12.3	9.1	8.9	2.7	8.2	3.3
17	17.0	7.8	18.1	12.4	10.3	2.8	13.1	6.6
18	21.8	12.9	28.2	4.7	17.0	8.5	23.7	3.6
19	25.0	15.3	32.2	18.3	17.4	6.9	22.7	7.0
Residence								
Urban	20.4	13.4	22.6	13.9	12.9	6.3	17.5	7.7
Non-urban	12.7	3.9	16.0	4.5	9.1	2.1	9.3	0.9
Province								
Western Cape	23.0	25.3	37.1	30.6	16.9	20.9	32.5	17.2
Eastern Cape	26.2	3.2	25.7	8.5	15.6	2.0	19.2	8.5
Northern Cape	28.7	18.7	26.4	29.8	23.0	10.0	21.3	15.2
Free State	9.5	8.7	21.2	12.2	4.3	1.2	12.7	2.1
KZN	8.5	2.9	17.0	6.0	4.0	1.0	14.8	2.3
North West	15.2	3.5	17.3	1.6	12.6	1.2	4.4	0.0
Gauteng	24.0	20.8	20.2	11.1	15.5	1.2	14.3	5.8
Mpumalanga	14.6	1.7	15.6	3.5	12.1	0.0	6.8	0.0
Limpopo	10.1	4.7	8.6	3.5	6.6	0.0	4.9	0.0
Population Group								
African	12.6	2.3	15.8	5.8	8.3	0.4	10.6	1.6
African urban	13.5	3.3	16.8	7.7	8.5	0.7	12.9	2.3
African non-urban	11.8	1.6	14.6	3.2	8.1	0.2	7.7	0.6
Coloured	28.8	27.2	48.8	47.6	25.9	16.9	47.4	34.2
White	42.8	47.6	68.5	15.6	19.0	27.3	36.3	10.3
Indian	36.0	15.3	55.2	24.4	21.5	2.4	35.0	15.3
Total	16.8	9.2	19.9	10.2	11.1	4.4	14.2	5.1

Source: Adapted from Department of Health (1998; 2003)

was estimated to contribute to 1.1% and 0.2% of all deaths, respectively; and, alcohol and illicit drug use combined were estimated to cause 7.4% and 1.3% of deaths, respectively.

Substance use plays a role in intentional and unintentional injuries, which are among the leading causes of death among young people globally and in South Africa: for example, road traffic accidents, self-inflicted injuries and violence (Donson, 2008; Patton et al, 2009). An investigation of 304 adolescent deaths in Johannesburg between 2001 and 2005 found that about 40% of homicide victims on whom BAC tests had been conducted were alcohol-positive (Swart, Seedat & Vellema, unpublished). Another study, of victims of non-natural deaths who were under 18 years, revealed positive blood-alcohol concentrations among 1.3% and 9.1% of cases examined in 1999 and 2000, respectively (Sukhai, 2002).

The role of substance use in injury is evident from studies among patients in trauma units. Parry et al (2004b) reported on the proportion of adolescent patients aged below 20 years in trauma units at state hospitals in Durban and Cape Town who tested positive for various drugs. Table 13.4 shows the proportions of those who tested positive for alcohol, cannabis, methaqualone, opiates and cocaine at the time of their admission. In Cape Town, the patients were most likely to test positive for alcohol, followed by cannabis and methaqualone. Just under one-third of patients had positive blood-alcohol levels. The Durban adolescents were more likely than those from Cape Town to have cannabis and methaqualone in their systems. In various cross-sectional studies conducted in South Africa, violence victimisation has been found to be associated with the use of psychoactive substances, such as alcohol in the case of sexual assault (King et al, 2004) and alcohol and other drugs in the case of more general forms of victimisation (eg, Morojele & Brook, 2006).

Alcohol and other drug use are also linked to crime among young people (Parry et al, 2004c). In their study of arrestees in holding cells, Parry et al found that young arrestees were more likely than their adult counterparts to test positive for the use of various illicit drugs.

A growing body of local and international literature suggests that alcohol and other drug use are associated with sexual risk behaviour among adolescents and youth. Studies in South Africa have indicated that adolescent alcohol and other drug users are more likely than non-users to be sexually active, and to have multiple sexual partners (Plüddemann et al, 2008; Mpofu et al, 2006; Taylor et al, 2003). However, the relationship with unprotected sex is less clear (Flisher & Chalton, 2001; Palen et al, 2006; Hendrikesen et al, 2007). Substance use is also associated with unplanned pregnancies among female adolescents (eg, Vundule et al, 2001).

Adolescents who use substances are more likely than their non-using counterparts to have current as well as long-term medical conditions, with this association being somewhat dependent on the type of drug used (eg, Kertesz et al, 2007; Mertens et al, 2007). In their study among adolescent patients in chemical dependency treatment clinics, Mertens et al found that adolescent substance use was associated with conditions including asthma, benign conditions of the uterus, injury and poisoning, sexually transmitted diseases (STDs), abdominal pain, sleep disorders and sinusitis (Mertens et al, 2007). Kertesz et al demonstrated a decline in the health status of a community-based sample of youth and young adult illicit drug users who were followed up over 15 years. There is also a growing

Table 13.4: Percentage of trauma unit patients (under 20 years) in Durban and Cape Town who tested positive for various drugs (1999–2001)

TYPE OF DRUG	DURBAN %	CAPE TOWN %
Alcohol	28.9	31.8
Cannabis	44.4	26.9
Methaqualone	28.6	15.4
Opiate	6.3	11.5
Cocaine	3.2	1.9

Source: Parry et al (2004b)

literature demonstrating the negative effects of substance use on brain development during adolescence (eg, White, 2003).

Substance use is commonly associated with other mental disorders (Degenhardt & Hall, 2006; Yen & Chong, 2006; Russell et al, 2008; Saban & Flisher, 2010). These associations are complex, and vary depending on factors such as the type of drug involved, the type of mental disorder, gender and developmental stage (Saban & Flisher, 2010; WHO, 2004). These authors note that substance use disorders may be a precursor to, or follow-on from the onset of other mental disorders, often resulting in a cyclical relationship between each disorder. Substance use and mental disorders may also co-occur (concurrently) due to a common underlying cause. When substance use disorders precede mental disorders, this may be due to a number of mechanisms. For example, substance use may give rise to, or 'induce', mental disorders, or it may exacerbate the course or severity of a pre-existing psychiatric disorder (Saban & Flisher, 2010).

Risk and protective factors

It is well recognised that substance use is associated with many interrelated risk and protective factors within various domains (NIDA, 1997; Pretorius et al, 1999; Parry et al, 2004c; Ostrowsky & Messner, 2005). 'Factors associated with greater potential for drug abuse are called "risk" factors' (NIDA, 1997:6). Protective factors are 'hypothesized to mediate or moderate the effects of risk exposure' (Catalano et al, 1996:431). As depicted in Table 13.5, risk and protective factors exist in a variety of domains, ranging from the individual to the environment. Because of the scope of this chapter, we will discuss only the main groups of factors. The following sections describe risk and protective factors for adolescent substance use within the following domains: individual, family, peers, school and community.

Individual

There are great individual differences in adolescents' vulnerability to substance use, abuse and substance use disorders (Jones, 2005; Eisenberg, 2005). Research studies have shown that certain personality characteristics are associated with substance abuse (Swendsen et al, 2002; Elkins et al, 2004). These characteristics include feelings of alienation, aggression,

Table 13.5: Risk and protective factors

DOMAIN	RISK FACTORS	PROTECTIVE FACTORS
Individual	Early aggressive behaviour; poor social coping skills; low self-esteem; rebelliousness; impulsive behaviour; antisocial behaviour; mental health problems; weak religious beliefs; stress reactions; feelings of rejection and failure; ego identity discomfort; high social and personal marginalism	Impulse control; good social coping skills; high self-esteem; compliance; cautious behaviour; pro-social behaviour; conformity; good mental health; strong religious beliefs; good coping skills; feelings of acceptance; feelings of achievement; ego identity acceptance
Family	Lack of parental supervision; ineffective parenting; parental neglect; lack of attachment; chaotic home environment; parental estrangement; weak family structure; low family connectedness; high familial stress; family members' substance use	Parental monitoring; disciplined parenting; parental support; mutual attachment; nurturing home environment; parental involvement; strong family structure; high family connectedness; low familial stress; family member non-substance use
Peer	Substance abuse; affiliation with deviant peers; learning difficulties; peer rejection; norms and values different from mainstream society; general tolerance of drug abuse	No substance abuse; affiliation with non-substance-using peers; academic competence; peer acceptance; norms and values similar to those held by mainstream society; acceptance of conventional norms regarding substance abuse
School	Drug availability; lack of sense of belonging; absenteeism; low educational opportunities; low educational or career goals	Anti-drug-use policies; sense of belonging; regular attendance; high educational opportunities; educational and career goals
Community	Poverty; availability; weak community attachments; lack of social support; limited involvement in community activities; low commitment; residential instability	Economically stable; strong community attachments; social support; involvement in community activities; high commitment; residential stability; low availability of drugs

Source: Adapted from National Institute on Drug Abuse (1997)

low levels of constraint and high stress reactions (Swendsen et al, 2002; Elkins et al, 2004). Other individual factors associated with adolescent substance use include rebelliousness, antisocial behaviour, tolerance of delinquent behaviour and impulsivity. In addition, individuals who have experienced marginalisation (for example, rejection and failure) and have negative feelings of self-worth often turn to drugs or alcohol in an attempt to assuage these emotions. While this use of drugs serves as a coping mechanism which results in temporary gratification, it generally averts the development of healthy coping mechanisms (Brook et al, 2005). Personal marginalisation can be the result of early life experiences,

which 'can sever individuals from norms or what is socially acceptable in their worlds' (Anderson, 1998:244).

As indicated in the previous section, mental disorders are strongly and in many cases bi-directionally, associated with substance use, abuse and substance use disorders among adolescents. In a recent review on comorbidity between substance use and mental disorders, anxiety, conduct and mood disorders were the disorders that were most frequently involved in studies where mental disorders were found to precede (and sometimes also come after) substance use disorders (Saban & Flisher, 2010). It is proposed that where substance use disorders precede mental disorders, substances are often used specifically to cope with the emotional and other problems arising from the mental disorder (Saban & Flisher, 2010).

Genetic factors have also been shown to be associated with substance use among adolescents (see Thatcher & Clark, 2008). According to Eisenberg (2005:3), 'Genes set the boundaries of the possible; environments parse out the actual.' Nature and nurture have a reciprocal relationship and the interaction between genetic and environmental influences is extremely complex. However, research indicates that the family environment plays such a profound role that when a child is brought up in destitute conditions the positive effects of genetic inheritance are often reduced (Jones, 2005; Eisenberg, 2005).

The main individual-level protective factors for drug use include high impulse control, good coping skills, good mental health and strong religious beliefs. Studies in South Africa have shown that regular attendance at religious services protects against substance use. Such behaviour seems to provide an element of social control, which serves as a strong protective factor against adolescent substance abuse and other deviant behaviour (Madu & Matla, 2003; Parry et al, 2004a).

Family

The individual cannot but be influenced by the environment in which he/she is raised, and various parental and familial factors have a protective or risk effect on adolescent substance abuse. Family risk factors for various forms of deviant behaviour include parental and sibling substance use, poverty, low educational levels, poor parenting practices, family stress and weak family structure (Jones, 2005; Anderson, 1998; Brook et al, 2006; NIDA, 1997). In families where drinking is normative, many adolescents model this behaviour. This modelling is further increased if alcohol consumption is also an accepted practice among their community and peer group (Onya, 2005; Parry et al, 2004a). Social learning theory (Bandura, 1977) maintains that individuals learn from observing, imitating or modelling the practices of others, and deviant or delinquent behaviour is learned in much the same way as pro-social behaviours. Drug-using behaviour is learned in interaction with others, and the lifestyle of peers, parents or other role models is often imitated (Anderson, 1998).

Family conflict is another risk factor for drug use. Madu and Matla (2003) found that adolescents who lived with families that had high levels of family conflict and a lack of emphasis on moral and religious values were more likely to engage in drug use behaviour. However, while problematic family relationships contribute to substance abuse among young people, a number of protective factors have also been identified. These include parental support, encouragement and acceptance (Pretorius et al, 1999). A sound family structure is a protective factor that provides essential support. Parents who monitor their

child closely and offer love and support are less likely to have children who engage in risky behaviour (Gibbons et al, 2004; Pretorius et al, 1999; Parry et al, 2004a). Parents who monitor their children's activities and stress the importance of academic achievement tend to have children who associate with conventional peer groups and avoid peer groups who are associated with a drug subculture (Gibbons et al, 2004).

Peers

Certain peer risk and protective factors are also associated with drug use. Peers play a major role in behaviour and the development of personality in adolescence (Brown, 2004; Engerman et al, 2006). Generally, adolescents have a strong need for group acceptance, support and belonging. The influence of the peer group is such that the individual often adopts the values and norms of the desired group and adapts his/her behaviour to conform to the group's behaviour. Adolescents seek approval and admiration by participating in group-approved behaviours, including substance use (Anderson, 1998; Steinberg & Monahan, 2007; Engerman et al, 2006). The peer groups with which young people associate may directly encourage drug use by reacting favourably to it (Krohn et al, 1996; Nkowane et al, 2004; Brook et al, 2005; Brook et al, 2006). However, while affiliation with peer groups may encourage deviant behaviour, affiliation with non-deviant peer groups may serve a protective role by providing a sense of acceptance and encouraging the adoption of norms and values which discourage delinquent, risky or substance use behaviours (Gardner & Steinberg, 2005). Interaction with peers who are learning-oriented, in particular, tends to provide adolescents with the prospect of forming positive peer models who will encourage the adoption of positive goals, such as academic achievement (Engerman et al, 2006).

School

Many factors within the school environment influence adolescents' use of drugs. They also influence their relationships with their peers, families and community (Flisher et al, 2003). Heavy drinking by adolescents has been found to be significantly associated with academic failure, absenteeism and risky sexual behaviour (Flisher et al, 2010). The majority of adolescents in South Africa complete primary school education. However, the challenge of remaining in school is often daunting among adolescents in poor communities, and many do not complete their education (Rutenberg et al, 2001). Various school factors are also protective factors against drug use. For example, when an adolescent feels a sense of connectedness and belonging to his/her school he/she is less likely to engage in risk-taking behaviour, such as substance use, and is more likely to develop a positive attitude to learning (Rutenberg et al, 2001).

Community

Various characteristics of communities serve as risk or protective factors for substance use among adolescents. Communities that offer formal activities such as sports clubs, study groups, church groups and youth groups provide important structures that enable young people to socialise in a healthy environment. This encourages community connectedness and social cohesion, which reduces the possibility of antisocial behaviour, including substance use (Rutenberg et al, 2001). Easy access to drugs (or high availability) at the

community level is a strong predictor of drug use. Parry et al (2004a) found that exposure to community drunkenness was a key predictor of public drunkenness. In addition, a high risk factor for drug use is the impoverished environment within which many adolescents live. In environments of pervasive poverty, many substance-abusing adolescents do not have a strong social support system, have few educational and employment opportunities, and generally experience limited parental guardianship (Nkowane et al, 2004; Flisher et al, 2010). Overall, individuals who are marginalised socially (that is, in a disadvantaged economic, social or cultural situation relative to mainstream society, major groups and/or other entities around them) are at greater risk of resorting to substance abuse to cope with their problems (Anderson, 1998).

Intervention approaches for addressing substance abuse among young people

Partly reflecting the multidisciplinary groups involved in the field of substance use, interventions to address substance use problems tend to be classified in varied ways (Ritter & McDonald, 2008). For example, some commentators distinguish between programmes focusing on the individual versus those focusing on the environment. Other schemes distinguish between total abstinence and harm reduction approaches, ie, approaches which seek to bring about total abstinence versus those focusing on reducing problems associated with substance use (and, possibly, levels of use as well). The traditional public health approach to prevention – very popular in the substance use field – distinguished between primary, secondary and tertiary prevention (Commission on Chronic Illness, 1957). This scheme refers to approaches that seek to prevent initiation of use/abuse, reduce use among those already involved, and treat substance use disorders, respectively. Despite the popularity of the latter approach, however, the Institute of Medicine (IOM, 1994) indicated a need for a better way of classifying interventions for mental disorders. It proposed the mental health intervention spectrum, according to which 'preventive interventions' are categorised separately from 'treatment' (therapeutic activities delivered to those who have the disorder in question) and 'maintenance' (interventions for illnesses that are ongoing, and adherence with long-term treatment and after-care services). Preventive interventions are then categorised into universal, selective and indicated approaches, which are distinguished on the basis of the target population for which the intervention is intended. In other words, universal, selective and indicated approaches are all forms of primary prevention in that they apply 'only to those interventions that occur before the initial onset of a disorder' (IOM, 1994:23). However, other commentators, such as Meili (2004; cited in EMCDDA, 2009), consider primary prevention to be akin to universal prevention, secondary prevention to be akin to either universal or selective prevention, and tertiary prevention to be akin to either selective or indicated prevention.

Universal prevention approaches

Universal prevention approaches are those that focus on whole populations. Universal programmes may take the form of education and persuasion strategies, regulatory strategies and harm reduction strategies. Universal prevention programmes for young people are

most likely to be implemented in community and school settings. Schools are the most common setting for such programmes since the majority of young people have access to schools. The Life Orientation curriculum in schools is one example of a universal approach since all school-going children are exposed to it. Chapter 14 in this volume discusses the effectiveness of three school-based prevention interventions in South Africa.

One group of universal interventions shown to have some success consists of regulatory (supply and demand reduction) interventions (Tombourou et al, 2007). These approaches make use of policy and legislative activities, coupled with enforcement of policies, mainly to bring about changes in environments. The most successful regulatory interventions have been shown to reduce both alcohol use and alcohol-related injuries, such as traffic collisions due to drunk-driving and alcohol-related violence. Alcohol prevention strategies for young people in particular include reducing the density of alcohol outlets and the opening times of alcohol-serving establishments in order to reduce availability (a common risk factor for alcohol use among adolescents); increasing prices through taxation; setting a minimum age for the purchase of alcoholic beverages (it is noteworthy that reductions in alcohol-related problems accompanied increasing the minimum age to 21 years in the United States); regulating the drinking context (although theoretically this approach should not apply to adolescents if they are prohibited from being in drinking settings in the first place); restrictions on alcohol marketing; and drink-driving counter-measures (Tombourou et al, 2007; WHO, 2007).

Education and persuasion approaches are very popular interventions, but have had varied degrees of success (WHO, 2007). The aim of such 'demand reduction' interventions is to educate and persuade people in order to reduce their demand for the use of alcohol and/or other drugs. The most successful education and persuasion approaches are media advocacy approaches, community mobilisation activities and some school-based interventions that have community and/or family components (Babor et al, 2003; Foxcroft et al, 2003). Less promising approaches, on the other hand, are education programmes in classroom settings, information campaigns, and the use of warning labels on alcohol beverage containers (Babor et al, 2003; Foxcroft et al, 2003). Counter-advertising strategies tend not to be effective, despite the impact of advertisement and marketing programmes on the alcohol use behaviours of young people (Smith & Foxcroft, 2009). The provision of information alone is not particularly effective in changing people's behavioural choices in the face of other powerful information sources and influences, such as community norms and messages emanating from the alcohol industry. Information sometimes brings about positive knowledge and attitudinal changes, but these changes do not necessarily translate into behaviour change (WHO, 2007; Babor et al, 2003).

Harm reduction strategies which take the form of universal prevention programmes are relatively rare, but the few that exist include the reversal of social norms programmes and expectancy challenge programmes (Neighbours et al, 2006). Reversal of norms programmes are most common among university students, and a Cochrane systematic review has shown some positive findings, particularly for interventions involving the provision of web/computer-based feedback (Moreira, Smith & Foxcroft, 2009). On the other hand, expectancy challenge programmes are relatively new, and their effectiveness is yet to be demonstrated systematically or to be replicated (Neighbours et al, 2006).

Selective intervention approaches

Selective approaches focus on individuals and/or subgroups which have a higher than average risk of developing substance use disorders. Consequently, they target populations, communities and groups deemed to be at higher risk of engaging in drug use. Examples of communities that may be targeted by selective prevention programmes include disadvantaged communities in which levels of drug use, exposure to drug use and availability are high, and law enforcement activity is lacking. Street children and 'delinquent gang' members are types of target groups to which such intervention approaches are most applicable. Programmes of this nature may be implemented in school, community and family settings, and, more specifically, they may be delivered in correctional facilities, shelters for street children and other services providing programmes for marginalised youth.

Some selective programmes use harm reduction strategies. For example, certain school-based interventions can be delivered to high-risk drinkers with a view to preventing/reducing drunk-driving and encouraging less harmful drinking styles (eg, McBride, 2005).

Indicated prevention approaches

Indicated approaches are focused on individuals who have been determined to be at risk for the development of a condition, illness or disorder in question, usually by means of screening activities. Such programmes may focus on those who may not have initiated use but are at high risk of doing so; who are manifesting early signs of a disorder; or who are assessed to have a high risk of doing so in the future. Often these approaches comprise early intervention activities and seek specifically to curb the progression of the drug use (IOM, 1994; EMCDDA, 2009). The types of intervention activities include motivational interventions, family-centred interventions and interventions with youth exhibiting 'delinquent or disruptive' behaviours (EMCDDA, 2009). Those who enter such programmes may do so voluntarily, be identified in emergency rooms/trauma centres, or they may be referred.

One harm reduction intervention that can be applied (and shown to be effective) as an indicated intervention involves needle or syringe exchange programmes. Such programmes are implemented to reduce transmission of HIV (and other viruses) among injection drug users (Tombourou et al, 2007). It is notable, however, that this approach may also be applicable to those injection drug users who have a substance use disorder, in which case the label 'indicated' to describe the programme would no longer apply.

In conclusion, there has been some research, albeit most of it from North America, Europe and Australia, from which we are able to see what is likely to work and what is not likely to work with regard to addressing substance use problems among young people. Specifically, regulatory interventions involving environmental or population approaches seem to be among the most effective and commonly replicated strategies. Other strategies that are effective are harm reduction and brief intervention strategies. Many communication and persuasion approaches are most effective in changing attitudes and knowledge regarding substances, but in general they are not so effective in changing behaviour. It is particularly noteworthy that there is a relative paucity of efficacy and effectiveness studies of prevention policies and programmes for South Africa, other middle-income countries and developing countries in general. However, a WHO expert committee concluded that many of the

findings of the studies can be translated to other settings, since many of the interventions are based on 'theories of action' (WHO, 2007:39) that have applicability across societies. On the other hand, effective interventions need to be adapted to the local settings in which they are implemented. The choice of which 'effective' intervention to import should be based on 'best practice' considerations, as well as on local needs, conditions, the nature, extent, patterns and types of substances used in the target community, the presence of competing influences (for example, from the alcohol industry) and social norms regarding substance use behaviours in the community in general and among young people in particular.

Adolescent substance abuse treatment services in South Africa

Despite the fact that at least a third of all clients treated within South African substance abuse treatment services are younger than 20 years (Plüddemann et al, 2009), treatment services for adults and adolescents remain largely undifferentiated. Adolescent-specific treatment programmes are a relatively new addition to the South African substance abuse treatment system, and remain limited. In the Western Cape province, which compared to the other provinces arguably has the highest level of problematic substance use among young people, there are only three registered adolescent-specific treatment programmes (together providing treatment slots for approximately 40 young people). Compared to the Western Cape, the other provinces have fewer adolescent-specific treatment services, with only one adolescent-specific programme present in KwaZulu-Natal and the central and northern regions of the country (comprising the Free State, Northern Cape, North West and Limpopo provinces), and none present in the Eastern Cape.

In addition, findings from recent audits of substance abuse treatment services in seven of the nine provinces reveal that more than half of the services surveyed treat adolescents alongside adults (Fakier & Myers, 2008; Myers & Fakier, 2007). Even where adolescent-specific treatment services do exist, these tend to be modelled on adult-oriented programmes (Fakier & Myers, 2008; Louw, 2004). This is cause for concern, given strong evidence that substance abuse treatment programmes designed for adults are not effective with, or appropriate for, adolescents. Firstly, adolescents who receive services alongside adults may be negatively influenced by adults with more chronic and severe substance use and other behavioural disorders. Secondly, adolescents have developmental and treatment needs that differ from adults (Deas et al, 2008). For instance, adolescents' reasoning, planning, judgment and decision-making abilities differ in key ways from adults who are cognitively more mature (Deas et al, 2008). Specifically, adults are more competent decision-makers than adolescents, and are more likely to seek advice and consider the pros and cons of each decision than adolescents (Halpern-Felsher & Cauffman, 2001). Moreover, adolescents process data differently from adults, with conditioned preference and aversion data showing adolescents to be more sensitive than adults to the positive rewarding properties of various drugs and natural stimuli, while less sensitive to the aversive properties of these stimuli (Doremus-Fitzwater et al, 2010). These cognitive differences need to be taken into account to ensure that treatment services are developmentally appropriate for adolescents.

Although there have been recent efforts to increase the availability of adolescent-oriented substance abuse treatment services in South Africa, the quality of these services is variable

(Louw, 2004; Myers, Burnhams & Fakier, 2010). In South Africa, many adolescent treatment programmes do not conform to evidence-based practices and models of care, offering generic life skills or religion-oriented programmes and/or a drug-free environment that serves as a 'vacation' from the adolescent's normal social environment. These approaches, however, fail to address the adolescent's core substance-related problems and to prevent a return to drug use post treatment (Fakier & Myers, 2008; Louw, 2004; Myers & Fakier, 2007), despite the fact that service providers can choose from a large number of evidence-based adolescent substance abuse treatment models that represent a variety of theoretical orientations, including family therapy, cognitive-behavioural treatment, behavioural therapy and 12-step approaches (Deas & Thomas, 2001).

Irrespective of their theoretical orientation, these evidence-based treatment approaches agree that treatment for adolescents should: (1) focus on achieving and maintaining abstinence; (2) address problems associated with substance use (such as psychiatric, family and academic difficulties); (3) be of sufficient duration and intensiveness; (4) be comprehensive and provide after-care or follow-up sessions; (5) be sensitive to cultural, racial and socio-economic factors; (6) include families; (7) promote pro-social activities and a drug-free lifestyle; and (8) be provided in the least-restrictive setting that is safe and effective. However, the extent to which these guiding principles are followed in South African treatment services is limited. South African research reveals that young people with substance use disorders are not being treated in an integrated, developmentally appropriate fashion. South African treatment services generally offer a restricted range of services and fail to address the psychiatric, family and educational problems, and sexual risk behaviours, that accompany adolescent substance use disorders (Myers, 2010; Myers & Fakier, 2009). For instance, most substance abuse services do not assess clients for mental health difficulties, and few treatment services offer integrated treatment for mental health and substance use disorders (Myers & Fakier, 2009). This failure to provide comprehensive treatment services is worrisome, as it has negative implications for treatment outcomes (Brannigan et al, 2004). Similarly, South African treatment services generally focus on the adolescent as the index patient, treating the adolescent in isolation from the family and other social networks (Fakier & Myers, 2008; Myers & Fakier, 2007). This is cause for concern, given that some of the most promising treatment models for adolescent substance use are family-based interventions with an ecological and developmental orientation. These include multidimensional family therapy (Liddle et al, 2001) and brief strategic family therapy (Santistiban et al, 2006).

These gaps in adolescent substance abuse treatment services highlight the need for ongoing efforts to improve service quality and effectiveness. Quality improvement efforts should concentrate on ensuring that adolescents with substance use disorders are provided with treatment services that are developmentally appropriate and based on sound clinical principles. Given the complexity of adolescent substance use disorders, efforts should focus on providing adolescents with a comprehensive menu of services that address the constellation of psychiatric, behavioural, family and academic problems that accompany substance use disorders. Such an integrated approach to substance abuse treatment will require strong partnerships and coordination between the social welfare, mental health, education and criminal justice systems.

Conclusion – agenda for research

Although South Africa has a relatively large amount of research on adolescent and youth substance use and abuse compared with other developing countries, there is still a need for much more. More research is required to better understand the epidemiology of substance use (including the prevalence and incidence of use of different drugs, and the consequences and risk and protective factors associated with drug use) and identify potentially effective interventions for addressing problem use.

Epidemiological studies typically take the form of household and school-based surveys. While undoubtedly useful, they are not ideal for assessing the extent of illegal drug use in particular, and are limited in that they rely on self-reports of behaviour which may often involve under-reporting. Innovative approaches are needed to address these challenges. For example, what methods may be culturally appropriate for yielding valid data? More research into objective methods for assessing substance use among adolescents and youth is called for.

Given that substance use is ever changing, there is a need for regular updated surveys to be able to track the nature, extent and patterns of drug use over time. Such studies could complement SACENDU, which, in its current form, only provides information on trends in drug use among treatment populations. It would be useful for governmental and other agencies to provide regular and consistent funding to repeat household and/or school surveys, as is the case in other parts of the world. The timely release of the results of such studies will make it more possible for responses to be developed on the basis of current and relevant information.

Despite their importance, very few longitudinal studies on alcohol and/or other drug use among young people have been conducted in South Africa. Among them are studies by Flisher and colleagues (2010), Patrick et al (2009), the Birth-to-Twenty study of the Human Sciences Research Council and one very small study conducted in Cape Town by Morojele et al (2001). Longitudinal studies are useful for at least two main reasons. Firstly, they are able to prospectively assess the course of substance use over time. Recent studies based on longitudinal investigations with multiple follow-ups have uncovered the existence of different trajectories of substance use behaviours between adolescence and adulthood (eg, Tucker et al, 2005). These suggest that somewhat different approaches are needed to address substance use problems for different trajectory groups. Such research is needed in South Africa. Secondly, longitudinal studies are able to disentangle the direction of relationships between variables that are uncovered in cross-sectional studies. Many cross-sectional studies have provided valuable information about psycho-social factors that are correlated with substance use, but they cannot indicate whether those factors precede and/or succeed drug use behaviours.

Much more intervention or evaluation research is needed to determine potentially effective intervention responses to substance abuse problems. Despite the importance of addressing such problems by using evidence-based approaches, many untested prevention and treatment interventions are implemented in South Africa (Burnhams, Myers & Parry, 2009).

Research on potentially effective universal, selected and indicated intervention strategies is also sorely needed. While much seems to have been learnt regarding regulatory

interventions, there is still a need for more studies to determine efficacious individual-level approaches, including school- and community-based interventions. The research seems to be particularly limited regarding the nature and effectiveness of selected and indicated prevention strategies.

Trauma units and other departments within the public health system are the places where first detection of substance use problems often occurs. Research is also needed to support the roll-out of early detection processes, screening of individuals with the potential for substance use problems, and referrals. Similar support should be available in school and other community settings.

The types of harm reduction strategies that may be useful to address local substance use-related problems are another important area of enquiry. Apart from needle exchange programmes (a prototype of harm reduction strategies) being well worth adopting, what other harm reduction strategies might be applicable specifically for South Africa's adolescents and youth, and might they work?

Research into various aspects of treatment for adolescent and youth substance use disorders is also needed urgently. Specifically, more studies are needed to determine the effectiveness of different treatment modalities (eg, brief, in-patient, out-patient) and approaches for addressing substance use disorders. In addition, the appropriateness of self-help programmes, such as those of the anonymous fellowships – Alcoholics Anonymous (AA), Narcotics Anonymous (NA) and Alateen for adolescents – is also worth investigating, particularly for people from resource-poor settings, for whom treatment access is limited. Also, an understanding of indigenous methods for addressing substance use problems may help to highlight potentially useful approaches. Adoption and implementation of unproven treatment approaches runs the risk of making no difference to, or even harming, recipients of such interventions.

In conclusion, a focus on substance use and abuse among adolescents and youth is crucial, given that first use and abuse of psychoactive substances often occurs and can become established for the long term during these developmental periods. Substances of various kinds have been used by members of different societies for many centuries, but are becoming increasingly used by young people. Unfortunately, psychoactive substance use is associated with many serious problems necessitating greater investment into research, evidence-based prevention efforts to reduce levels of use and/or problems, and treatment programmes for those in need.

References

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders*. 4th edition. Washington, DC: American Psychiatric Association.

Anderson, T.L. (1998). A cultural-identity theory of drug abuse. *Sociology of Crime, Law and Deviance*, 1:233–62.

Babor, T., Caetano, R., Casswell, S., Edwards, G., Giesbrecht, N., Graham, K., Grube, J., Gruenwald, P., Hill, L., Holder, H., Homel, R., Österberg, E., Rehm, J., Room, R. & Rossow, I. (2003). *Alcohol: No Ordinary Commodity*. Oxford: Oxford University Press.

Bandura, A. (1977). *Social Learning Theory*. New York: General Learning Press.

Behrendt, S., Wittchen, H.-U., Höfler, M., Lieb, R. & Beesdo, K. (2009). Transitions from first substance use to substance use disorders in adolescence: Is early onset associated with a rapid escalation? *Drug and Alcohol Dependence*, 99(1–3):68–78.

Brannigan, R., Schackman, B.R., Falco, M. & Millman, B. (2004). The quality of highly regarded adolescent substance abuse treatment programs: results of an in-depth national survey. *Archives of Paediatrics and Adolescent Medicine*, 158(9):904–909.

Brook, J., Morojele, N., Pahl, K. & Brook, D. (2006). Predictors of drug use among South African adolescents. *Journal of Adolescent Health*, 38(1):26–34.

Brook, J.S., Morojele, N.K., Brook, D.W. & Rosen, Z, (2005). Predictors of cigarette use among South African adolescents. *International Journal of Behavioural Medicine*, 12(4):207–17.

Brown, B. (2004). Adolescents' relationships with peers. In R. Lerner & L. Steinberg (eds), *Handbook of Adolescent Psychology*. 2nd edition. New York: Wiley; pp 363–94.

Burnhams, N., Myers, B. & Parry, C. (2009). To what extent do youth-focused prevention programmes reflect evidence-based practices? Findings from an audit of alcohol and other drug prevention programmes in Cape Town, South Africa. *African Journal of Drug & Alcohol Studies*, 8(1):1–8.

Catalano, R.F., Kosterman, R., Hawkins, J.D., Newcomb, M.D. & Abbott, R.D. (1996). Modeling the etiology of adolescent substance use: a test of the social development model. *Journal of Drug Issues*, 26(2):429–55.

Commission on Chronic Illness. (1957). *Chronic Illness in the United States*. Vol. 1. Cambridge, MA: Harvard University Press.

Deas, D., Gray, K. & Upadhyaya, H. (2008). Evidence-based treatments for adolescent substance use disorders. In R.G. Steele, T.D. Elkin & M.C. Roberts (eds). *Handbook of Evidence-based Therapies for Children and Adolescents: Bridging Science and Practice*. New York: Springer; pp 429–44.

Deas, D. & Thomas, S.E. (2001). An overview of controlled studies of adolescent substance abuse treatment. *American Journal on Addiction*, 10(2):178–89.

Degenhardt, L. & Hall, W. (2006). Is cannabis use a contributory cause of psychosis? *Canadian Journal of Psychiatry*, 51(9):556–65.

Department of Health. (1998). *South African Demographic and Health Survey 1998*. Available from: http://www.doh.gov.za/facts/1998/sadhs98/; accessed 11 August 2011.

Department of Health. (2003). *South African Demographic and Health Survey 2003*. Available from: http://www.doh.gov.za/facts/sadhs2003/main.html; accessed 11 August 2011.

Donson, H. (ed.) (2008). *A Profile of Fatal Injuries in South Africa, 2003*. 9th Annual Report of the National Injury Mortality Surveillance System. Parow: MRC-UNISA Crime, Violence and Injury Lead Programme.

Doremus-Fitzwater, T.L., Varlinskaya, E.I. & Spear, L.P. (2010). Motivational systems in adolescence: possible implications for age differences in substance abuse and other risk-taking behaviors. *Brain and Cognition*, 72(1):114–23.

Elkins, I.J., McGue, M., Malone, S. & Iacono, W.G. (2004). The effect of parental alcohol and drug disorders on adolescent personality. *American Journal of Psychiatry*, 161(4): 670–76.

Engerman, K., Bailey, U. & Oyemade, J. (2006). Family decision-making style, peer group affiliation and prior academic achievement of African American students. *Journal of Negro*

Education, Available from: http://findarticles.com/p/articles/mi_qa3626/is_200607/ai_n17177851/; accessed 18 February 2010.

Eisenberg, L. (2005). Are genes destiny? Have adenine, cytosine, guanine and thymine replaced Lachesis, Clotho and Atropos as the weavers of our fate? *World Psychiatry*, 4(1):1–8.

European Monitoring Centre for Drugs and Drug Addiction. (2008). *Selected Issue – Drugs and Vulnerable Groups of Young People*. Luxembourg: Office for Official Publications of the European Communities. Available from: http://www.emcdda.europa.eu/attachements.cfm/att_64250_EN_EMCDDA_SI08_vulnerable-young.pdf; accessed 15 February 2010.

European Monitoring Centre for Drugs and Drug Addiction. (2009). *Preventing Later Substance Use Disorders in At-Risk Children and Adolescents: A Review of the Theory and Evidence Base of Indicated Prevention*. Luxembourg: Office for Official Publications of the European Communities. Available from: http://www.emcdda.europa.eu/publications/thematic-papers/indicated-prevention; accessed 15 February 2010.

Fakier, N. & Myers, B. (2008). *Audit of Substance Abuse Treatment Facilities in Free State*, *Limpopo*, *Mpumalanga*, *North West and Northern Cape (2007–2008)*. Parow: Medical Research Council.

Flisher, A.J. & Chalton, D.O. (2001). Adolescent contraceptive non-use and covariation among risk behaviors. *Journal of Adolescent Health*, 28(3):235–41.

Flisher, A.J., Mathews, C., Mukoma, W., Ahmed, N. & Lombard, C.F. (2006). Secular trends in risk behaviour of Cape Town Grade 8 students. *South African Medical Journal*, 96(9):982–87.

Flisher, A.J., Parry, C.D.H., Evans, J., Muller, M. & Lombard, C. (2003). Substance use by adolescents in Cape Town: prevalence and correlates. *Journal of Adolescent Health*, 32(1):58–65.

Flisher A.J., Townsend, L., Chikobvu, P., Lombard, C. & King, G. (2010). Substance use and psychosocial predictors of high school dropout in Cape Town, South Africa. *Journal of Research on Adolescence*, 20(1):237–55.

Foxcroft, D.R., Ireland, D., Lister-Sharp, D.J., Lowe, G. & Breen, R. (2002). Primary prevention for alcohol misuse among young people. Cochrane Database Syst. Rev.:, Issue 3, Art No. CD003024. DOI: 10.1002/14651858.CD003024. (This version first published online: 22 July 2002 in Issue 3, 2002.)

Fulkerson, J.A., Harrison, P.A. & Beebe, T.J. (1999). DSM-IV substance abuse and dependence: are there really two dimensions of substance use disorders in adolescents? *Addiction*, 94(4):495–506.

Gardner, M. & Steinberg, L. (2005). Peer influence on risk taking, risk preference, and risky decision making in adolescence and adulthood: an experimental study. *Developmental Psychology*, 41(4):625–35.

Gibbons, F.X., Gerrard, M., Cleveland, M.J., Wills, T.A., Brody, G. (2004). Perceived discrimination and substance use in African American parents and their children: a panel study. *Journal of Personality and Social Psychology*, 86(4):517–29.

Halpern-Felsher, B. & Cauffman, E. (2001). Costs and benefits of a decision: Decisionmaking competence in adolescents and adults. *Journal of Applied Developmental Psychology*, 22(3):257–73.

Hendriksen, E.S., Pettifor, A., Lee, S.-J., Coates, T.J. & Rees, H.V. (2007). Predictors of condom use among young adults in South Africa: the Reproductive Health and HIV Research Unit National Youth Survey. *American Journal of Public Health*, 97(7):1241–48.

Institute of Medicine. (1994). *Reducing risks for Mental Disorders: Frontiers for Preventive Intervention Research*. Washington, DC: National Academy Press. Available from: http://www.nap.edu/catalog/2139.html; accessed 11 August 2011.

Jernigan, D.H. (2001). *Global Status Report: Alcohol and Young Poeple*. Geneva: World Health Organization.

Jones, C.M. (2005). *Genetic and Environmental Influences on Criminal Behaviour*. Available from: http://www.personalityresearch.org/papers/jones.html; accessed 30 December 2009.

Kertsesz, S.G., Pletcher, M.J., Safford, M., Halanych, J., Kirk, K., Schumacher, J., Sidney, S. & Kiefe, C.I. (2007). Illicit drug use in young adults and subsequent decline in general health: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Drug and Alcohol Dependence*, 88(2–3):224–33.

King, G., Flisher, A.J., Noubary, F., Reece, R., Marais, A. & Lombard, C. (2004). Substance abuse and behavioral correlates of sexual assault among South African adolescents. *Child Abuse and Neglect*, 28(6):683–96.

Kleintjies, S, Flisher, A.J., Fick, M., Railoun, A., Lund, C., Molteno, C. & Robertson, B. (2006). The prevalence of mental disorders among children, adolescents and adults in the Western Cape, South Africa. *South African Psychiatry Review*, 9(3):157–60.

Krohn, M.D., Lizotte, A.J., Thornberry, T.P., Smith, C. & McDowall, D. (1996). Reciprocal causal relationships among drug use, peers, and beliefs: a five-wave panel model. *Journal of Drug Issues*, 26(2):405–28.

Liddle, H.A., Dakof, G.A., Parker, K., Diamond, G.S., Barrett, K. & Tejeda, M. (2001). Multidimensional family therapy for adolescent drug abuse: results of a randomized clinical trial. *The American Journal of Drug and Alcohol Abuse*, 27(4):651–88.

Louw, S. (2004). Opvoedkundig-sielkundige Criteria vir die Evaluering van Rehabilitasie-prograamme vir Dwelafhanklike Adolessente in Suid-Afrika. Unpublished doctoral thesis. Johannesburg: Rand Afrikaans University.

Madu, S.N. & Matla, M.P. (2003). Correlations for perceived family environment factors with substance use among adolescents in South Africa. *Psychological Reports*, 92(2):403–15.

Martin, C.S. & Winters, K.C. (1998). Diagnosis and assessment of alcohol use disorders among adolescents. *Alcohol Health and Research World*, 22(2):95–105.

McBride, N. (2005). The evidence base for school drug education interventions. In T. Stockwell, P.J. Gruenwald, J.W. Toumbourou & W. Loxley (eds). *Preventing Harmful Substance Use: The Evidence Base for Policy and Practice*. Chichester: Wiley; pp 101–12.

Mertens, J.R., Flisher, A.J., Fleming, M.F. & Weisner, C.M. (2007). Medical conditions of adolescents in alcohol and drug treatment: comparison with matched controls. *Journal of Adolescent Health*, 40(2):173–79.

Moreira, M.T., Smith, L.A. & Foxcroft, D. (2009). Social norms interventions to reduce alcohol misuse in University or College students. Cochrane Database Syst. Rev.: Issue 3. Art. No. CD006748. DOI: 10.1002/14651858.CD006748.pub2.

Morojele, N.K. & Brook, J.S. (2006). Substance use and multiple victimisation among adolescents in South Africa. *Addictive Behaviours*, 31(7):1163–76.

Morojele, N.K., Parry, C., Ziervogel, C. & Robertson, B. (2001). Adolescent alcohol misuse: correlates and implications. *African Journal of Drug & Alcohol Studies*, 1(2):110–24.

Mpofu, E., Flisher, A.J., Bility, K., Onya, H. & Lombard, C. (2006). Sexual partners in a rural South African setting. *AIDS Behavior*, 10(4):399–404.

Myers, B. (2010). Limited access to HIV risk reduction services in South African substance abuse treatment services. *Drugs: Education, Prevention & Policy*, 17(6):749–61.

Myers, B., Burnhams N.H. & Fakier, N. (2010). Monitoring and evaluation of substance abuse services in South Africa: implications for policy and practice. *International Journal of Mental Health and Addiction*, 8(4):557–65.

Myers, B. & Fakier, N. (2007). *Audit of Substance Abuse Treatment Facilities in KwaZulu-Natal and Gauteng, 2007*. Technical Report. Cape Town: Medical Research Council.

Myers, B. & Fakier, N. 2009. Provision of mental health services in South African substance abuse treatment facilities. *International Journal of Mental Health and Addiction*, 7(3):441–49.

Myers, B., Siegfried, N. & Parry, C.D.H. (2003). Over-the-counter and prescription medicine misuse in Cape Town, South Africa. Findings from specialist treatment centres. *South African Medical Journal*, 93(5):367–70.

National Institute on Drug Abuse. (1997). *Preventing Drug Use Among Children and Adolescents. A Research-Based Guide for Parents, Educators and Community Leaders*. 2nd edition. National Institute of Health. Available from: http://www.drugabuse.gov/pdf/prevention/RedBook.pdf; accessed 11 August 2011.

Neighbours, C., Larimer, M.E., Lostutter, T.W. & Woods, B.A. (2006). Harm reduction and individually focused alcohol prevention. *International Journal of Drug Policy*, 17(4):304–309.

Nkowane, M.A., Rocha-Silva, L., Saxena, S. & Mbatia, J. (2004). Psychoactive substance use among young people: findings of a multi-center study in three African countries. *Contemporary Drug Problems*, 31:329–57.

Onya, E.H. (2005). A qualitative study of home-brewed alcohol use among adolescents in Mankweng District, Limpopo Province, South Africa. In N.S. Madu & S. Govender. *Mental Health and Psychotherapy in Africa*. Sovenga, South Africa: UL Press of the University of Limpopo; pp 291–307.

Ostrowsky, M.K. & Messner, S.F. (2005). Explaining crime for a young adult population: an application of general strain theory. *Journal of Criminal Justice*, 33(5):463–76.

Palen, L.A., Smith, E.A., Flisher, A.J., Caldwell, L.L. & Mpofu, E. (2006). Substance use and sexual risk behavior among South African eighth grade students. *Journal of Adolescent Health*, 39(5):761–63.

Parry, C.D.H., Morojele, N.K., Saban, A. & Flisher, A.J. (2004a). Brief report: social and neighbourhood correlates of adolescent drunkenness: a pilot study in Cape Town, South Africa. *Journal of Adolescence*, 27(3):369–74.

Parry, C.D.H., Myers, B., Morojele, N., Flisher, A.J., Bhana, A., Donson, H. & Plüddemann, A. (2004b). The South African Community Epidemiology Network on Drug Use (SACENDU) Project: monitoring trends in adolescent alcohol and other

drug use in three sentinel sites in South Africa (1997–2000). *Journal of Adolescence*, 27(4):429–40.

Parry, C.D.H., Plüddemann, A., Louw, A. & Leggett. T. (2004c). The 3-Metros Study of Drugs and Crime in South Africa: findings and policy implications. *American Journal of Drug and Alcohol Abuse*, 30(1):167–85.

Patton, G.C., Coffey, C., Sawyer, S.M., Viner, R.M., Haller, D.M., Bose, K., Vos, T, Ferguson, J. & Mathers, C.D. (2009). Global patterns of mortality in young people: a systematic analysis of population health data. *Lancet*, 374(9693):881–92.

Patrick, M.E., Collins, L., Smith, E., Caldwell, L., Flisher, A. & Wegner, L. (2009). A prospective longitudinal model of substance use onset among South African adolescents. *Substance Use and Misuse*, 44(5):647–62.

Plüddemann, A., Dada, S., Williams, Y., Bhana, A., Pereira, T., Carelsen, A., Kitleli, N., Gerber, W., Rosslee, C., Parry, C.D.H. & Fourie, D. (2009). *Monitoring Alcohol and Drug Abuse Trends in South Africa.* Proceedings of SACENDU Report-Back Meetings, May 2009: July–December 2008 (Phase 25). Parow: Medical Research Council.

Plüddemann, A., Flisher, A.J., Mathews, C., Carney, T. & Lombard, C. (2008). Adolescent methamphetamine use and sexual risk behaviour in secondary school students in Cape Town, South Africa. *Drug and Alcohol Review*, 27(6):687–92.

Plüddemann, A., Flisher, A.J., McKetin, R., Parry, C. & Lombard, C. (2010). Methamphetamine use, aggressive behavior and other mental health issues among high school students in Cape Town, South Africa. *Drug and Alcohol Dependence*, 109(1–3):14–19.

Pretorius, J.W.M., Ferreira, G.V. & Edwards, D.N. (1999). Crisis phenomena among African adolescents. *Adolescence*, 34(133):139–47.

Reddy, S.P., James, S., Sewpaul, R., Koopman, F., Funani, N.I., Sifunda, S., Josie, J., Masuka, P., Kambaran, N.S. & Omardien, R.G. (2010). *Umthente Uhlaba Usamila – The South African Youth Risk Behaviour Survey 2008.* Cape Town: South African Medical Research Council.

Reddy, S.P., Panday, S., Swart, D., Jinabhai, C.C., Amosun, S.L., James, S., Monyeki, K.D., Stevens, G., Morojele, N., Kambaran, N.S., Omardien, R.G. & Van der Borne, H.W. (2003). *Umthenthe Uhlaba Usamila – The South African Youth Risk Survey 2002*. Cape Town: Medical Research Council.

Reddy, P., Resnicow, K., Omardien, R. & Kambaran, N. (2007). Prevalence and correlates of substance use among high school students in South Africa and the United States. *American Journal of Public Health*, 97(10):1859–64.

Ritter, A. & McDonald, D. (2008). Illicit drug policy: scoping the interventions and taxonomies. *Drugs: Education, Prevention and Policy*, 15(1):15–35.

Roberts, R.E., Roberts, C.R. & Xing, Y. (2007). Rates of DSM-IV psychiatric disorders among adolescents in a large metropolitan area. *Journal of Psychiatric Research*, 41(11):959–67.

Russell, K., Donna, M., Dryden, D.M., Liang, Y., Friesen, C., O'Gorman, K., Durec, T., Wild, T.C. & Klassen, T.P. (2008). Risk factors for methamphetamine use in youth: a systematic review. *BMC Pediatrics*, 8:48.

Rutenberg, N., Kehus-Alons, C., Brown, L., Macintyre, K., Dallimore, A. & Kaufman, C. (2001). *Transitions to Adulthood in the Context of AIDS in South Africa: Report of Wave 1*. Durban: University of Natal, School of Developmental Studies.

Saban, A. & Flisher, A.J. (2010). The association between psychopathology and substance use in young people: a review of the literature. *Journal of Psychoactive Drugs* 42(1):37–47.

Santisteban, D.A., Suarez-Morales, L., Robbins, M.S. & Szapocznik, J. (2006). Brief strategic family therapy: lessons learned in efficacy research and challenges to blending research and practice. *Family Process*, 45(2):259–71.

Smith, L.A. & Foxcroft, D.R. (2009). The effect of alcohol advertising, marketing and portrayal on drinking behaviour in young people: systematic review of prospective cohort studies. *BMC Public Health*, 9:51.

Steinberg, L. & Monahan, K.C. (2007). Age differences in resistance to peer influence. *Developmental Psychology*, 43(6):1531–43.

Sukhai, A. (2002). Alcohol-related mortality Durban (1999–2000). Unpublished presentation. Available from: http://www.sahealthinfo.org/violence/durbanalcohol.pdf; accessed 11 August 2011.

Swart, L.-A., Seedat, M. & Vellema, J. (n.d.). Adolescent homicide victimisation in Johannesburg, South Africa. Institute for Social and Health Sciences, University of South Africa. Available from: http://www.mrc.ac.za/crime/adolescent.pdf; accessed 15 January 2010.

Swendsen, J.D., Conway, K.P., Rounsaville, B.J. & Merikangas, K.R. (2002). Are personality traits familial risk factors for substance use disorders? Results of a controlled family study. *American Journal of Psychiatry*, 159(10):1760–66.

Taylor, M., Dlamini, S.B., Kagoro, H., Jinabhai, C.C. & De Vries, H. (2003). Understanding high school students' risk behaviors to help reduce the HIV/AIDS epidemic in KwaZulu-Natal, South Africa. *Journal of School Health*, 73(3):97–100.

Thatcher, D.L. & Clark, D.B. (2008). Adolescents at risk for substance use disorders. *Alcohol Research & Health*, 31(2):168–76.

Toumbourou, J.W., Stockwell, T., Neighbors, C., Marlatt, G.A., Sturge, J. & Rehm, J. (2007). Interventions to reduce harm associated with adolescent substance use. *Lancet*, 369(9570):1391–401.

Tucker, J.S., Ellickson, P.L., Orlando, M., Martino, S.C. & Klein, D.J. (2005). Substance use trajectories from early adolescence to emerging adulthood: a comparison of smoking, binge drinking, and marijuana use. *Journal of Drug Issues*, 35(2):307–31.

United Nations Office on Drugs and Crime. (2009). *World Drug Report 2009*. Vienna: United Nations Publications. Available from: http://www.unodc.org/documents/wdr/WDR_2009/WDR2009_eng_web.pdf; accessed 15 February 2010.

Vundule, C., Maforah, F., Jewkes, R. & Jordan, E. (2001). Risk factors for teenage pregnancy among sexually active African adolescents in Cape Town: A case control study. *South African Medical Journal*, 91(1):73–80.

White, A. (2003). Substance use and adolescent brain development. *Youth Studies Australia*, 22(1):39–45.

World Health Organization (2004). *Global Status Report on Alcohol 2004*. Geneva: World Health Organization, Department of Mental Health and Substance Abuse.

World Health Organization Expert Committee on Problems Related to Alcohol Consumption. (2007). WHO Technical Report Series, No. 944. Second report. Geneva: World Health Organization. Available from: http://www.who.int/substance_abuse/expert_committee_alcohol_trs944.pdf; accessed 15 February 2010.

Yen, C.-F. & Chong, M.-Y. (2006). Comorbid psychiatric disorders, sex, and methamphetamine use in adolescents: a case-control study. *Comprehensive Psychiatry*, 47(3):215–20.

York, J.L., Welte, J., Hirsch, J., Hoffman, J.H. & Barnes, G. (2004). Association of age at first drink with current alcohol drinking variables in a national general population sample. *Alcoholism: Clinical and Experimental Research*, 28(9):1379–87.

14 Evaluated interventions to prevent substance abuse among young South Africans

Cleo Protogerou, Alan J. Flisher and Neo K. Morojele

Introduction

In 2001 the South African Department of Education introduced the mandatory Life Orientation learning area for students from Grade 1 to Grade 12. Life Orientation encourages healthy lifestyles by promoting general health and wellbeing, but also targets drug use, sexuality, and socio-emotive skills development. Yet few schools prioritise Life Orientation, and teachers tend to implement its components in a personalised and unsystematic fashion (Smith et al, 2008). This intervention is one of many that deal with substance use prevention programmes for young people in South Africa. But the prevention efforts have had variable degrees of success, highlighting the necessity to subject these to rigorous evaluation.

What follows is a critical review of the five existing published substance abuse prevention interventions for young people in South Africa. All of these interventions incorporated an aspect of evaluation. Their small number allows for an in-depth assessment, wherein theory, design, methodology and results are considered in detail. We set out by clarifying basic theoretical and methodological issues of substance abuse interventions, and then proceed with the review itself.

Theoretical underpinnings of preventive interventions

Up to today, substance abuse preventive efforts have been based on *abstinence* or, less commonly, *harm minimisation* rationales. Abstinence interventions promote cessation messages and primarily include teaching developmentally appropriate life skills (ie, Life Skills Training, or LST) that have been shown to potentially inhibit, or delay the onset of, substance use. In young people, such skills include: identifying and dealing with emotions; managing anger, frustration, and stress; learning how to communicate and negotiate effectively; rational decision-making; developing assertiveness and peer pressure resistance; and acquiring drug-related information. LST espouses a generic cognitive-behavioural skills training approach to prevention, suggesting that successful intervention effects can be obtained in relation to all substances, all risk-taking activities, all school settings (eg, rural, urban), all recipients (eg, children, adolescents), and by all primary providers (eg, social scientists, peer leaders, teachers, project staff). LST programmes are generally long-term: the main intervention lasts about one school year (15–17 class periods), with at least another year of booster sessions (Botvin & Griffin,

2001). LST interventions are based on a theoretical framework which incorporates elements from social learning theory (Bandura, 1977), general problem behaviour (Jessor & Jessor, 1977), self-derogation (Kaplan, 1980), peer pressure (Oetting & Beauvais, 1987) and persuasion (McGuire, 1968). This framework conceptualises substance use as a behaviour resulting from an interaction between individual personality characteristics and environmental and social influences. For example, some people (but not others) succumb to social influences from media outputs that sensationalise and normalise drugs, or from significant others who use and hold favourable attitudes towards drugs. The impact of social factors is likely to be stronger on individuals with poor social or personal skills, low self-esteem and psychological distress. Historically, LST interventions have been the most widely employed, with reported successful outcomes (eg, Botvin et al, 1990; 1995a), but recent evidence from systematic reviews has cast doubts upon their effectiveness (Foxcroft et al, 2003; Resnicow et al, 2008).

Contrary to abstinence interventions, harm minimisation (HM) interventions are based on the assumption that preventing or eliminating substance use entirely is unrealistic. As a result, HM strategies focus on reducing the harmful effects of substance use (Resnicow et al, 2008). An example of an HM intervention implemented on a national level is in the Netherlands, where marijuana is legally sold and consumed in 'koffeeshops', although sales to non-adults and purchases over 30 grams per person are not allowed (Drucker, 1995). By legalising marijuana, the Dutch government managed to reduce harm by inspecting dose quality and controlling the quantity that can be legally purchased by citizens.

On a smaller scale, and directed towards young people, HM interventions can involve brief interventions, such as motivational enhancement interventions. Brief interventions are usually one to five sessions, and have the singular focus of targeting substance use behaviours in a systematic way (O'Leary Tevyaw & Monti, 2004). Basic strategies of brief HM interventions include clear directions as to how to minimise harm (eg, avoiding addiction by irregular use, reducing substance dose, limiting the times and locations where substance use occurs, preventing progression to additional substances), as well as motivational enhancement/interviewing. Motivational enhancement (ie, increasing readiness to enact behavioural change) and interviewing (Miller & Rollnick, 2002) include ways of relating to others, as well as a set of techniques. Such techniques include an empathetic and non-judgmental stance, listening reflectively, rolling with resistance, avoiding argument, creating discrepancy and promoting self-efficacy for change. For example, a brief HM interventionist would typically establish an atmosphere of collaborating equals, by accepting the individual and not entering into debates concerning their beliefs and behaviours. Instances of anger or defensiveness (ie, resistance) from the individual would prompt the interventionist to change strategy (ie, rolling with resistance). Motivational enhancement techniques can be embedded in any type of intervention, but they tend to have a prominent position in the briefer HM approaches (O'Leary Tevyaw & Monti, 2004). Motivational enhancement and interviewing is grounded in robust psychological theories and strategies: client-centred therapy principles (Rogers, 1957), cognitive-behaviour therapy principles applied to substance abuse (Monti et al, 1989), social learning theory (Bandura, 1977), and the trans-theoretical model of behaviour change (Prochaska, DiClemente & Norcross, 1992). Although a relative newcomer in

the substance prevention arena, evaluations of brief motivational HM interventions have yielded promising results in reducing substance use (eg, Borsari & Carey, 2000; Wechsberg et al, 2008) and substance-related problems (Baer et al, 2001).

Methodological issues: building effective interventions

Nation et al (2003) drew from guidelines put forth by drug research and prevention organisations, such as the National Institute on Drug Abuse (NIDA) and the Centre for Substance Abuse Prevention (CSAP), and used a review-of-reviews strategy across four problem behaviour domains, to identify nine characteristics consistently linked to effective prevention interventions for young people. Effective programmes:

- Are comprehensive (combine different types of interventions at various settings)
- Include varied teaching methods (interactive instruction, hands-on experience, role playing, discussion groups)
- Provide sufficient dosage (appropriate duration of intervention gauged to the problem behaviour and the recipient in question; booster sessions)
- Are scientifically justified (based on empirically tested theories and techniques)
- Foster positive relationships (promote quality relationships among peers and with at least one adult)
- Are appropriately timed (as a general rule, the earlier, the better, starting from preschool)
- Are socio-culturally relevant (tailored to the needs of the specific culture, community and target population)
- Involve well-trained staff (select appropriate staff and provide additional training and support)
- Are evaluated (assess whether the intervention reached its goals).

Evaluation design issues

The success of an intervention will, partially at least, depend on the type of design researchers adopt. Effective interventions aim for designs that take steps to ensure valid results (ie, results that are accurate in terms of the extent to which they correspond with reality). The validity of results is enhanced for designs that encompass high levels of experimental control, high response rates, low attrition rates and random allocation of groups to treatments. The strongest intervention design is a randomised controlled trial (RCT), in which individuals or groups are randomly allocated to receive an intervention or a control condition. Validity can be threatened when the unit of treatment allocation (usually the class or community) is different from the unit of analysis (usually the individual). In such a situation, participants from a specific setting (eg, class) tend to be more similar to one another, compared to participants of a different setting, and the within-setting correlation of the data adds another component of the variability to the intervention group mean (Foxcroft et al, 2003). This within-setting correlation is indexed by the intraclass correlation coefficient (ICC), and unless the ICC is taken into consideration the intervention effects will be biased positively in relation to the magnitude of the ICC and to the number of participants in each setting (Donnor et al,

1990). Acceptable ICC values in school-based preventive interventions are thought to range from .001 to .05 (Hamilton et al, 2005).

A high response rate at baseline provides some indication that the intervention was designed in such a way that participants found it interesting, engaging and resonant with their reality. High response rates also reflect adequate recruiting and sampling procedures, as well as participant trust in the investigators.

The attrition, or dropout, rate is the number or proportion of participants who did not receive the intervention or were not assessed at follow-up. A high attrition rate (approximately 20% and higher) threatens the validity of the study but can be partially addressed in the statistical analysis. For example, an intention-to-treat-analysis partially deals with attrition, and is considered to be the optimal way to obtain the outcome of an intervention (Foxcroft et al, 2003). An intention-to-treat analysis would include (in the final statistical analysis) data from all participants present at baseline. Conceptually, this is important for public health research and policy, because the health of the population needs to be considered as a whole, even if a proportion of the target population did not receive, for any number of reasons, the intervention.

In an attempt to find a scheme of enhancing the external and internal validity of interventions, a group of health experts (eg, Egger, Jüni & Bartlett, 2001; Moher, Schulz & Altman, 2001) devised a comprehensive guide incorporating items that should be taken into consideration when designing and reporting interventions. This scheme is known as the CONSORT Statement (Consolidated Standards of Reporting Trials), and was originally devised with RCTs in mind, but it is also relevant to other designs, such as factorial, equivalence and cluster designs. The CONSORT statement provides guidance to interventionists by providing clear and explicit ways of strengthening intervention designs. Although the studies reviewed in this chapter have incorporated several of the CONSORT items, no reference is made to the statement itself. Thus, our aim here is to increase awareness of the existence of the CONSORT statement (see Table 14.1) and urge researchers to follow it in future research.

Fidelity versus adaptation

Programme developers aim to have their interventions implemented with fidelity (ie, the degree to which programme providers implement programmes as intended by programme developers). Fidelity can be operationalised in terms of:

- Programme *adherence* (the extent to which intervention methods and strategies are consistent with original programme scripture);
- *Dose* (the amount of content participants received);
- *Quality* (the extent to which the provider maintains a theoretical ideal in relation to programme delivery);
- *Differentiation* (the extent to which intervention components can be consistently differentiated from one another);
- *Participant responsiveness* (the extent to which participants are engaged in the activities) (Dane & Schneider, 1998; Dusenbury et al, 2003).

Substance abuse prevention studies indicate that the more completely and consistently an intervention is implemented, the more likely students are to reduce their drug use

Table 14.1: Essential items to be included and reported in interventions

INTRODUCTION
1. Theoretical and empirical background of intervention, and explanation of rationale 2. Objectives, aims and hypotheses of the study 3. Ethics procedures of the study 4. Eligibility criteria of participants and description of the settings from which data were collected 5. Detailed description of the intervention 6. Detailed description of the processes of intervention administration 7. Clear definition of primary and secondary outcome measures 8. Explanation of sampling and recruiting procedures 9. Method of sample randomisation and restriction (eg, clustering, stratification) 10. Method of implementation of random allocation sequence (eg, numbered containers), and clarification if sequence was concealed until the moment of the intervention 11. Information about who generated allocation sequence, participant enrolment and participant assignment to groups 12. Information about whether participants, those administering the intervention and those assessing the results were blinded to group assignment; blinding success 13. Explanation of statistical analyses employed
RESULTS
14. Report of flow of participants through each stage (numbers of participants randomly assigned, those receiving intended treatment, completing the study protocol and analysed for the primary outcome), and deviations from original protocol 15. Statement of times between recruitment and follow-up 16. Number of participants in each group included in each analysis and whether the analysis was by 'intention-to-treat'. If possible, provide absolute numbers instead of percentages (eg, 10 of 20, not 50%) 17. For each primary and secondary outcome (and per group), a summary of results, the estimated effect size, and its precision (eg, 95% confidence interval) 18. Multiplicity (reporting any additional statistical analyses, including subgroup analyses and adjusted analyses) 19. Disclosure of all important adverse events or side effects in each intervention group
DISCUSSION
20. Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes 21. Generalisability (external validity) of the trial findings 22. Interpretation of the results in the context of current evidence

Adapted from the CONSORT Statement (Moher, Schulz & Altman, 2001)

(Botvin et al, 1990b; Resnicow et al, 1993). In reality, however, programme providers tend to alter and adapt the intervention according to their needs, beliefs, desires and other prevailing circumstances. Ringwalt et al (2003) reported that about a fifth of teachers do not use the intervention manual at all, while only about 15% indicate following the manual closely. A main reason for this 'tension' between programme fidelity and adaptation is that interventions do not always resonate with the culture or the setting of the target population. As a result, programme developers have come to recognise the role of culture-relevant factors in prevention, and have been making efforts to culturally ground their interventions (ie, ensure that the intervention reflects the language, thoughts, beliefs, values, customs and actions of recipients). Indeed, research has shown that interventions are unlikely to be successful without 'ownership', or enthusiastic participation and commitment from the recipient environment (Holleran Steiker et al, 2007). Currently, concerns have shifted from whether interventions ought to be adapted to how they can best be adapted to fit the host environment. Although traditionally programme developers engaged key stakeholders and other 'experts' in the process of cultural adaptation, recent studies suggest that the best way to create a truly culturally grounded intervention is to use the target population as the primary expert (Holleran Steiker, 2008). Clearly, members of the target population provide the most accurate accounts of their current language styles, their way of life, attitudes, behaviours and experiences (Holleran Steiker, 2006; Shapiro, 1985). Thus a 'tension' has been found to exist between intervention fidelity and adaptation, with research efforts directed towards identifying optimal ways of adapting the original programme to the target populations' needs, without compromising programme efficacy.

Evaluation

Evaluation enables programme developers, and all interested parties, to assess whether the intervention is successful, that is, whether it accomplished its pre-set goals. People tend to think about evaluation mostly in terms of outcome assessment (eg, whether the intervention managed to prevent or modify the behaviour in question), but outcome success or failure is directly linked to programme design and implementation. Thus, ideally, evaluation occurs at all stages of the intervention, from its initial conception to the final results. Turner et al (1989) describe evaluation as a dynamic and systematic process wherein the investigator constantly examines who did what, how and why. Besides estimating the efficacy of an intervention, additional reasons for conducting an evaluation consist of enabling replication by interested researchers, and providing accountability to invested governmental agencies, funding bodies and the general public. In this chapter, we review evaluated interventions, following a comprehensive process and logic, as described by Flisher et al (2008). Specifically, we will check if and how authors conducted:

- formative evaluation (eg, programme creation; adequacy of theoretical and empirical basis, and design; cultural adaptation)
- input evaluation (eg, adequacy of resources, such as funding, number and training of staff, facilities and equipment, that were allocated)
- process evaluation (eg, assessment of actual implementation)

- output evaluation (eg, documentation of measurable products, such as number of sessions, community and staff meetings, number of participants; extent of programme coverage)
- outcome evaluation (eg, intervention efficacy, in terms of modifying behaviour, attitudes, norms as intended).

The present review

To be included in this review, a study had to be published and incorporate some element of evaluation. Study participants comprised young people from educational and non-educational settings. Studies that focused on heavy users of substances, as well as specific occupations/settings – for example, sex workers, truck drivers, mineworkers, incarcerated individuals – were excluded, in order to emphasise 'young people' in general. We conducted the search using the databases Medline, PubMed and Social Sciences Index, and through the platforms Science Direct and Google Scholar. We browsed all the publications of the South African Medical Research Council (MRC). We checked the reference lists of studies for further articles, and conducted hand searches of the journals *Addiction*, *Addictive Behaviors*, *Substance Use and Misuse*, *Drug and Alcohol Dependence*, *Health Education Research*, *Journal of Youth and Adolescence* and *South African Journal of Psychology*. Moreover, we approached, via email and personal communication, researchers who are actively involved in the prevention field. Search items included combinations of the following: 'drug', 'alcohol', 'substance', 'adolescence', 'youth', 'young people/adults', 'students', 'intervention', 'programme', 'curriculum', 'education', 'prevention', 'reduction', 'promotion', 'cessation', 'evaluation', 'efficacy', 'effectiveness', 'comparison', 'trial' and 'South Africa'. Boolean operators (AND, OR) and truncation (*) were used.

Results and discussion

Description of interventions (see also Table 14.2)

Five studies met the selection criteria (Karnell et al, 2006; Cupp, et al, 2008; Resnicow et al, 2008; Smith et al, 2008; Wechsberg et al, 2008). The first four studies were primary prevention interventions, while the fourth study was a secondary prevention intervention. Although the studies varied in terms of focus, target audience and behaviour (see Table 14.2), they were similar in that they drew from interventions originally created in countries other than South Africa. Specifically, the interventions of Karnell et al and Cupp et al promoted abstinence messages and LST to Grade 9 township adolescents from Pietermaritzburg, KwaZulu-Natal, and were based on an American alcohol and HIV prevention community programme (Project Northland: Perry et al, 1996). Resnicow et al compared the efficacy of an American LST abstinence module with an Australian HM intervention (KEEP LEFT; Hamilton et al, 2005), targeting smoking and other drug use, in Grade 8 and 9 black and coloured students from KwaZulu-Natal and the Western Cape. Smith et al targeted substance use and sexual risk in Grades 8 and 9 students from schools of Mitchell's Plain

Table 14.2: Interventions

AUTHORS	SAMPLES	GENERAL DESCRIPTION	TECHNIQUES	FOCUS	DESIGN	CULTURAL ADAPTATION
Cupp et al., 2008	Grade 9 students from near Pietermaritzburg township N=1 095 Attrition: unspecified Median age=15	Alcohol & HIV prevention. Based on LST approach	School setting Peer & teacher-led discussions, role-playing, group assignments, monologues	Cessation	Cluster randomised controlled trial 4–6 & 15–18 months follow-up	An adaptation process is reported for the questionnaire Unclear if/how cultural adaptation was performed
Karnell et al., 2006	Grade 9 students from Pietermaritzburg townships N=661 Attrition=19% Median age=16	Alcohol & HIV prevention Based on LST approach	School setting Peer-led discussions Group Assignments	Cessation	Pre-post-quasi-experimental with comparison group 5-month follow-up	An adaptation process is reported for the questionnaire Unclear if/how cultural adaptation was performed
Resnicow et al., 2008	Grade 8 & 9 students from KwaZulu-Natal and Western Cape N=5 226 Attrition=11% Mean age=14	Substance use reduction and prevention Based on LST & HM approaches	School setting Teacher-led activities	Reduction/ cessation/ harm minimisation	RCT 2-year follow-up	Yes
Smith et al., 2008	Grade 8 & 9 students from Mitchell's Plain, Cape Town N=2 383 Attrition=50% Mean age=14	Substance use and sexual risk prevention Based on LST approach	School setting Teacher-led activities	Cessation/ reduction	Quasi-experimental, with control group Non-probability sampling 5 waves, 2.5 year follow-up	Yes
Wechsberg et al., 2008	Black & coloured high-risk adult women from Cape Town townships N=60 Attrition=2% Mode age=19	Substance use & sexual risk reduction Based on HM approach	Community setting Individual or group interviews	Reduction/ harm minimisation	1-group, before-after-no control Randomisation for intervention format 1-month follow-up	Yes

township, Cape Town, by using three American modules that combined abstinence and HM messages. The modules included curricula that targeted students' leisure time activities (TimeWise: Caldwell, 2004), LST and sexual risk-taking. Wechsberg et al implemented a brief HM substance use intervention, in individual and group format, to high-risk black and coloured women (ie, substance users) from Cape Town townships, which was based on the American Women's Co-Op (Lyles et al, 2007).

With the exception of Resnicow et al, the interventions addressed both substance and sexual risks on the basis of hypothesised links between sexual risk-taking and substance use, as observed in the international (eg, Donovan & Jessor, 1985) and South African (eg, Flisher et al, 1996; Mpofu et al, 2006; Palen et al, 2006) literature.

Evaluation of interventions

Theoretical and empirical basis

The interventions of Karnell et al and Cupp et al espoused a LST preventive approach, primarily promoting abstinence and substance use cessation. Smith et al's programme incorporated both abstinence and HM rationales. Contrary to this, Wechsberg et al adopted a brief HM approach. Until recently, the LST approach was considered the 'silver bullet' of prevention, with most interventions utilising LST strategies. Certainly, LST interventions have provided favourable outcomes (eg, Botvin et al, 1990; Botvin et al, 1990b), but recent reports have cast doubts on their preventive abilities. Specifically, Foxcroft et al (2003) suggested that although Botvin et al (1995a; 1995b) reported statistically significant and long-term LST intervention effects on substance abuse prevention, these results rested on a problematic design (only high-fidelity sample, receiving 60% of intervention, was assessed). When Foxcroft et al conducted an intention-to-treat re-analysis of Botvin et al's (1995a; 1995b) data, no statistically significant intervention effects were retrieved. Moreover, a number of studies (eg, Donaldson et al, 1994; Elder et al, 1993) found that LST did not mediate substance use among young people who received such interventions, and one study reported drug use increase in high-risk female adolescents (Palinkas et al, 1996). The study of Resnicow et al tested the efficacy of an LST approach against an HM approach, and is thus exceptional in terms of providing an empirical justification of using either approach in South African students. Although Resnicow et al found statistically significant effects for both types of intervention, the results differed for gender and race. For 30-day substance use, the HM programme appeared to be more effective for boys, whereas LST appeared somewhat more effective for girls. Resnicow et al found that participants disagreed with LST messages that promoted abstinence, but embraced HM messages that emphasised autonomy around substance use decisions. HM messages may have particularly resonated with boys, for whom assertiveness, independence and rebellion may be more central to substance use. In relation to race, the HM intervention was more effective for black students, whereas the LST was more effective for coloured ones. Although explaining race effects is more difficult, the authors put forth the possibility that coloured students are more influenced by European cultures promoting individuality, whereas black students are more influenced by indigenous principles of 'Ubuntu-humaneness and interconnectedness' (Resnicow et al, 2008:241).

With the exception of Resnicow et al, the remaining interventions view risk-taking as part of a syndrome of risk behaviours (Cooper, Wood & Orcutt, 1996; Donovan & Jessor, 1985; Flisher et al, 1996; Mpofu et al, 2006; Palen et al, 2006), that is, a general propensity for some people to engage in a range of risk behaviours. According to this approach, health risk behaviours are regarded as interrelated rather than independent activities (eg, substance use is assumed to be linked to sexual risk-taking), which, conceptually, justifies creating interventions that target more than one behaviour. This notwithstanding, many studies report no association between substance use and sexual risk-taking (eg, Crosby et al, 2003; Flisher & Chalton, 2001; Leigh, 2002; Kingree & Betz, 2003), and the syndromic approach, although intuitively appealing, is not adopted by the majority of health-risk investigators. A syndromic approach to risk-taking downplays the existence of factors that influence some risk-taking behaviours but not others. For example, relationship characteristics and the

premium placed on love and trust have been established as important mediators, and/or moderators, of sexual risk-taking (Rhodes & Cusick, 2002; Sheeran, Abraham & Orbell, 1999), but not of substance use. Relevant to this, Wechsberg et al were careful to point out that their reported relationship between substance abuse and sexual risk-taking was mediated by partner abuse, interpersonal conflict and sexual disinhibition. Smith et al found that, although their programme had some encouraging effects on substance use, no such effects were found for sexual risk-taking.

On taking a closer look at the original interventions the South African ones were based upon, we found that the interventions of Karnell et al and Cupp et al used an abstinence-based community programme (Project Northland: Perry et al, 1996), which has been reported to have diminished effectiveness. Specifically, Project Northland was evaluated by Foxcroft et al and by Perry et al as ineffective in sustaining longer-term outcomes. Moreover, Project Northland had no effects on actual/intended alcohol use for those who had started drinking, but only on the whole sample, or on abstainers. Thus, the potential exists that Project Northland promotes an abstinence message to those who do not really need it. Finally, the community aspect of this intervention (ie, incorporating school, family and community activities) was not implemented in the South African version.

Design

We found that the study of Resnicow et al had the strongest design. Resnicow et al conducted a between-schools RCT that stratified by socio-economic status, randomised to one of three groups (12 LST schools versus 12 HM schools versus 12 control schools) and had two post-tests at Grades 8 and 9 (two-year follow-up). Measurement was done by a self-reported questionnaire, adapted from prior studies conducted in South Africa, with acceptable Cronbach's alpha levels (0.73 to 0.93). The authors adopted an intention-to-treat approach, thus enhancing quality and validity of data: for the two post-test assessments, only individuals who were in the school at the beginning of Grade 8 and who completed the baseline evaluation were asked to complete questionnaires. The statistics were appropriate to the design, with unit of allocation and unit of analysis being the same (school level). Still, ICC levels were high: 0.40 for binge drinking, 0.05 for marijuana, 0.14 for smoking, which the authors attributed to high cultural homogeneity at randomisation. The response rate was high (93%) and attrition was acceptable (11%). Ethics procedures included institutional approval and confidentiality/anonymity assurances.

Smith et al adopted a quasi-experimental, between-schools design, with non-probability purposive sampling: the same four schools that participated in a previous pilot became the treatment schools; five more new schools were selected, and subjectively matched to the treatment schools, to be the control schools. This type of purposive sampling is susceptible to carry-over effects, which here mean that participation at the pilot phase might enhance performance at the intervention phase. The results from five times of data collection, with six-month intervals, are reported in this study. The response rate was high (98%), but attrition was also high (about 50% from baseline to final measurement). The authors discuss how attrition was statistically dealt with (multiple imputation), but they do not describe how dropouts differed from intervention participants. Measurement was obtained through a self-administered survey by the use of PDAs (Personal Digital Assistants). Scale

development was not described and alpha levels were not provided. The authors did not clarify if the unit of allocation and unit of analysis were the same, and an intention-to-treat analysis was not conducted. The ICC value was noted as 'very low' (Smith et al, 2008: 319). The ethics procedures included institutional approval and informed consent of educators, principals, and guardians.

Karnell et al used a quasi-experimental, between-schools design that randomised to either intervention (n = 3) or control (n = 2) schools. Measurement was carried out by a self-reported questionnaire, with alpha levels ranging from 0.52 to 0.89. The authors did not adopt an intention-to-treat approach. Moreover, the unit of allocation was the school but the unit of analysis was the individual. The response rate was not provided, and attrition was high (19%) for the five-month follow-up. No information was provided as to how attrition was dealt with. Ethics procedures included institutional approval, but no information is given about informed consent.

Cupp et al employed a cluster randomised controlled trial, with randomisation occurring at the school level (follow up measurements at 4–6 months and 15–18 months). Four schools received the intervention, and four served as controls. Measurement was initially conducted via self-reported questionnaires, but due to practical difficulties, such as crowding and noise, it was continued via PDAs. Alpha levels ranged between 0.27 and 0.44. An intention-to-treat approach was not followed, and the unit of allocation (school) differed from the unit of analysis (individual). Response rates, attrition rates and ICC coefficients were not reported for the study. Ethics procedures included consent forms (completed by parents) and assent forms (completed by students), but the institution that granted ethics clearance was not indicated.

Wechsberg et al conducted a one-group, before-after field experiment, with no control. Participants were stratified by race, and randomly assigned to receive an individual or a group intervention format. Care was taken to demographically match interviewer and interviewee. Measurements were obtained via self-reported, paper and pencil, face-to-face interviews. The response rate was almost 100%, and attrition was only 2% at the one-month follow-up. Statistical analyses were appropriate for the design – the unit of allocation and unit of analysis were both on the individual level. The ethics procedures included institutional approval and participant informed consent.

We note that only Wechsberg et al provided an account of the recruitment process, while none of the four studies mentioned whether the voluntary/freedom to withdraw aspect was explained, and if participants were debriefed.

Cultural adaptation

All authors reported culturally adapting their interventions, although this was done with great variation and with different degrees of success. It seems that Resnicow et al conducted the most relevant cultural adaptation, by using students as the main sources of information. Through focus groups, students provided in-depth information about perceived norms, motivations and gender-specific aspects of substances and their use. Although teachers, too, contributed to clarifying gender and cultural factors, their input was mostly on teaching/delivering aspects of the curriculum. The use of students as main sources of information adds significantly to the inherent validity of the intervention. In addition, local curriculum

writers, graphic designers and creators of the original programmes provided their input and expertise. Curricula were pre-tested with teachers, revised, and pilot-tested by teachers with students as participants. Students were also asked to make language adaptations to the intervention, and although English was the primary language of the curriculum, there were optional Zulu and Xhosa variations.

Smith et al conducted extensive cultural adaptation procedures, but we feel that adaptation could have relied more on students' reports. To elaborate, the initial cultural modification to match South African realities was based on the research team's subjective judgments, which was followed by a second cultural adaptation centred on teacher and key community stakeholder input. Although teachers' opinions are necessary for issues regarding optimal programme implementation, it is unlikely that they will provide realistic accounts of adolescent drug-related attitudes and experiences without being influenced by moralistic attitudes. Community stakeholders' input may enable programme sustainability, but may not provide valuable input for intervention content. Student input was taken during and after intervention implementation. Thus, students were not actively involved in the initial stages of programme construction, but in the evaluation of the programme (eg, clarifying the degree to which the programme met their needs).

The intervention Wechsberg et al used was initially adapted for black South African women in Pretoria and was further adapted for substance-using black and coloured women in the Western Cape province by in-depth interviews and focus groups. The authors do not describe in detail the nature of these interviews and focus groups.

Karnell et al report that their field trial was '… adapted from an American model' (Karnell et al, 2006: 297), but provide no information about their actual process of cultural adaptation. The authors only provide information about developing the questionnaire that was used in the survey. The same stands for the Cupp et al study, which is, in essence, a continuation of the Karnell et al study (Karnell et al's intervention was the pilot for the Cupp et al study).

In assessing these intervention formation processes, only one study (Resnicow et al) was very well executed and provided a clear theoretical and empirical justification of testing an HM against an LST approach; adopted a robust design (RCT); conducted appropriate statistical analyses, while taking into account attrition, intention-to-treat and ICC; and conducted a realistic cultural adaptation using students as the main source of information. The remaining three interventions are weaker either in terms of theory (Karnell et al and Smith et al espouse a predominately LST, abstinence-promotion, general-problem behaviour model, which in recent years has received criticism), design (lack of RCTs, no control group, absence of random sampling), methodology (different unit of allocation and measurement, absence of intention-to-treat, high attrition) or absence of/insufficient cultural adaptation.

Process evaluation: considering procedure of implementation, fidelity, inputs and outputs

Although interventionists, in general, might overlook this aspect of evaluation (Flisher et al, 2008), three out of four interventions (Resnicow, et al, Smith et al, and Wechsberg et al) invested considerably in evaluating process. In assessing the studies, we find that

Resnicow et al and Smith et al did the best process evaluations and provided evidence of fidelity. Specifically, Resnicow et al provided a clear and detailed description of the process of implementation. They provided the inputs (eg, a three-day teacher training course on theory and practice; recruitment of local writers and graphic designers; provision of workbooks and manuals; teacher feedback and technical assistance) and the outputs (eg, hours of inputs and number of student sessions). They also demonstrated fidelity by taking steps to enhance quality of teacher implementation (eg, rating and providing feedback on teachers' classroom management, ability to answer questions, adherence to plan), estimating dose and intensity (eg, auditing workbooks to see amount of lesson taught) and showing students' ability to differentiate components of an intervention. Smith et al adopted a similar approach on presenting and monitoring process. For example, Smith et al reported inputs (educator three-day training workshops on programme theory and the importance of accomplishing fidelity and process evaluation) and fidelity were determined via qualitative focus groups with teachers (as explicated in Wegner et al, 2008), revealing that teachers tended to improvise rather than deviate from the curriculum. Wechsberg et al also clearly described process, and provided hours of staff work and training and sessions with participants. Notably, intervention inputs included monetary and other incentives at baseline (ie, gift vouchers to local supermarkets, transportation) and at follow-up (ie, vouchers, transportation, a risk-reduction kit, T-shirt, certificate of attendance). Such incentives not only enhance participation attendance, but also boost participants' feelings of being respected and taken care of. Wechsberg et al did not evaluate fidelity. Finally, Karnell et al (and Cupp et al, as reported in Karnell et al) provided a vague process of implementation, which was scattered in several places in the article. Very limited information was provided about how the intervention was monitored and how peer leaders were trained, with no assessment of inputs or outputs. Reports on fidelity were mostly anecdotal: for example, '… all teachers delivered the full curriculum in the prescribed time … teachers expressed satisfaction with the programme' (Karnell et al, 2006: 304). Another problem is that Karnell et al and Cupp et al describe/evaluate aspects of the survey (ie, data collection) but not the intervention *per se*.

To recap, at least three of the interventions made considerable efforts to evaluate process of implementation, thus adding to and demonstrating the strengths therein (see also Table 14.3 for a comparison of the evaluations discussed in this section).

Outcome evaluation: intervention effects

Out of the four interventions, only Wechsberg et al's short HM programme demonstrated clear and statistically significant intervention effects, but the lack of a control group needs to be taken into consideration. In assessing the variables directly linked to substance use, large and statistically significant decreases were found in the mean number of days of past month self-reported use of alcohol and illicit substances, for both black and coloured women, at a one month follow-up. In assessing variables indirectly linked to substance use, coloured women (but not black) demonstrated reductions in the number of times they used alcohol and other drugs before or during sex. Additionally, findings suggest that a brief intervention, regardless of format (ie, group or individual), may reduce substance abuse and other risk-taking, in both coloured and black women, at least within a short follow-up period.

Table 14.3: Evaluations

AUTHORS	SAMPLES	TYPES OF EVALUATION	FACTORS EVALUATED	RESULTS
Cupp et al, 2008	Staff, students & teachers	Process outcome	■ Student understanding and satisfaction with programme & peer leaders ■ Student privacy & honesty ■ Teacher satisfaction & delivery pace ■ Alcohol-related attitudes, intentions, refusal self-efficacy, perceived peer-drinking, 'ever used alcohol'	■ Majority of students were satisfied, understood the programme, found it easy, realistic & reported privacy & honesty ■ Teachers were satisfied ■ Statistically significant intervention effects were found for alcohol refusal self-efficacy
Karnell et al, 2006	Staff, students & teachers	Process outcome	■ Student understanding and satisfaction with programme & peer leaders ■ Student privacy & honesty ■ Teacher satisfaction & delivery pace ■ Frequency/quantity of alcohol use, alcohol-related problems, attitudes, refusal self-efficacy	■ Majority of students were satisfied, understood the programme, found it easy, realistic & reported privacy & honesty ■ Teachers were satisfied ■ No statistically significant intervention effects
Resnicow et al, 2008	Staff, students, teachers, local writers, graphic designers, experts	Process input Output outcome	■ Teacher implementation, training, manuals, workbooks, hours invested, dose, intensity, adherence to plan, aim and component differentiation ■ Past-month substance use ■ Perceived harm of use, refusal skills, attitudes	■ Good process of implementation, high fidelity ■ No statistically significant intervention effects for substance use modification, but effects were differentially established for race and gender
Smith et al, 2008	Staff, teachers, students, key stakeholders, youth developmental specialties	Process input Output outcome	■ Teacher implementation, training, manuals, technical assistance, hours/sessions invested, dose, intensity, adherence to plan, message & component differentiation ■ Lifetime, past-month and frequency of substance use	■ Good process of implementation, high fidelity ■ Modest intervention results for substance use prevention; better results for female participants
Wechsberg et al, 2008	Staff & members of target group	Process input Output outcome	■ Staff training, monetary expenses, risk-reduction kit, T-shirt, certificate, hours/sessions invested ■ Use of substances, use of substances prior to & during sexual intercourse	■ Good process of implementation, fidelity was not assessed ■ Large, statistically significant reductions in mean number of days of substance use ■ Both individual and group formats were effective. Reductions in the number of times coloured women used substances prior to/during sex

Smith et al established encouraging, albeit modest, statistically significant intervention effects for substance use, especially for girls, at a 2.5-year follow-up. Although both males and females receiving the programme reported a smaller increase in recent cigarette and alcohol use, compared to the controls, programme effects on cigarette and alcohol use were stronger for girls (non-users at baseline). In addition, the girls who received the programme were less likely to initiate marijuana use, compared to their male counterparts. The programme had no effect on sexual risk-taking. Smith et al's explanation of the modest (or no) intervention effects included problems with operationalisation and measurement of variables relating to sexual risk, non-probability randomisation, not obtaining data from dropouts, and reliance on self-reported behaviour as a measure of change.

Resnicow et al found no statistically significant intervention effects for past month cigarette, marijuana, binge drinking and hard drugs, at a two-year post-intervention. In addition, no statistically significant intervention effects were obtained in relation to participant perceived harm of ever used a substance, perceived refusal skills or attitude towards substance use. Still, statistically significant intervention effects were found for gender and race; the HM intervention was more effective for males and black students, whereas the LST intervention was more effective for females and coloured students. The authors attribute the null effect to the high ICC/homogeneity of race, the absence of booster sessions and potential flaws in adaptation procedures. Also, the stringent (yet appropriate) intention-to-treat approach may have masked favourable outcomes. Resnicow et al re-ran the statistical analysis without an intention-to-treat design and found statistically significant intervention effects for smoking and for all the psycho-social variables.

Karnell et al did not find statistically significant intervention effects for any alcohol-related variables (ie, frequency and quantity of use, refusal self-efficacy and attitudes) or for HIV-related psycho-social variables (eg, condom use attitudes and self-efficacy), at the five-month follow-up. An intervention effect was found for alcohol use concurrent with sexual intercourse for students who were virgins at pre-test. The authors report that 'intervention students who had not had sex at the time of pre-test, were less likely to drink or indicate that their partners would drink, before or during the last time they had sex' (Karnell et al, 2006: 304). However, potential conceptual problems arise here, as it is unclear if (and how many) students had sex at post-test. Intervention students who were virgins at pre-test were 61 in total, but there is no indication of how many had sex at post-test. Karnell et al attribute null intervention effects to reliance on self-reports, lack of privacy due to space restrictions and the use of English, instead of Zulu, as the intervention/survey language.

Cupp et al provided statistically significant intervention effects for one (out of the four) alcohol-related variables, namely alcohol refusal self-efficacy, for the 4–6 and 15–18-month follow-ups. Specifically, students in the intervention groups showed a greater increase in their ability to refuse alcohol, than their control counterparts, but the intervention had no effect on alcohol-related attitudes, intentions, or for 'ever using alcohol'.

To conclude, outcome evaluation showed that intervention effects were modest at best for the primary interventions, with the exception of Wechsberg et al, who clearly demonstrated the benefits of using a brief intervention to reduce substance abuse (for a comparison of the interventions, see Table 14.3).

Final remarks

Overall, findings suggest that, despite considerable efforts and resources invested in their development and implementation, South African primary prevention interventions for young people were only moderately successful in reducing or stopping substance use. The intervention that showed the most statistically significant reductions (Wechsberg et al) was a secondary prevention intervention (participants were chosen on the basis of symptomatology, ie, drug use). We will now discuss possible reasons for the observed outcomes and make suggestions for future research.

Follow-up assessment times differed in the reviewed interventions, and the shortest follow-up (one month in the Wechsberg et al study) yielded the most statistically significant outcomes. It is unclear whether these favourable outcomes would be obtained, and maintained, in longer-term assessments.

Except for Wechsberg et al, the interventions reviewed here were based on long-term LST strategies that incorporated abstinence/cessation messages. Additionally, except for Resnicow et al, the reviewed interventions targeted sexual risk-taking in conjunction with substance use. Historically, preventive efforts have been based on the LST approach, but recent evidence has questioned its widespread use, on the basis of conceptual and empirical considerations (Foxcroft et al, 2003; O'Leary Tevyaw & Monti, 2004). Conceptually, promoting abstinence, or refusal, messages to young people, and in particular to those who have already started using substances, may make no sense to them. Global and South African statistics report that young people use legal and/or illegal substances. Attempting to implement abstinence, or a more stringent 'just say no' philosophy, can be perceived as unrealistic and offensive by the user. For example, a 'just-say-no' philosophy implies that drug use is dependent on personal choice and responsibility, which consequently reprimands the individual for use and consequences of use. Such an approach to drug use and its prevention will ultimately prompt defensive responses from a section of the population, potentially sabotaging intervention efforts from the start. Moreover, advocating personal responsibility and choice in substance use is inconsistent with what is known about the neurophysiology and neuropharmacology of drug use. Specifically, substance use may well be 'a personal choice' to begin with, but it progressively becomes habitual/automatic, reflecting underlying neuropharmacological and physiological mechanisms that underpin instrumental learning, or addiction (Nestler, 2004). It is now known that the action of the neurotransmitter dopamine on neuron receptors in the nucleus accumbens of the brain plays a critical role in establishing and maintaining substance use, or addiction (Tomkins & Sellers, 2001). This involuntary, or addictive, component, distinguishes substance use from other risk-taking activities, and further questions the general problem-behaviour approach, as well as the use of generic cognitive LST interventions. While some evidence supports a general propensity of people to engage in more than one risk activity (Jessor & Jessor, 1977), this approach overlooks fundamental variations among the nature of risk-taking activities, and the differential underlying motivations of the people involved. Consequently, using LST approaches targeting more than one risk-taking activity, and in particular substance use and sexual risk, may not be warranted, conceptually and empirically. This notwithstanding, we have not come across data suggesting that combined

interventions harm the participants. In addressing LST approaches specifically, however, data exists suggesting ineffectiveness in terms of outcomes (Foxcroft et al, 2003) and adversity in a sample of high-risk female adolescents (Palinkas et al, 1996). Data from the reviewed studies did not provide support for combining sexual risk and substance use interventions. For example, Smith et al managed to modify substance use but not sexual risk-taking.

The current alternative to LST programmes are the brief harm-minimisation interventions, which also incorporate skills training but emphasise empowering and motivating the individual to change, without promoting moralistic, zero-tolerance messages. HM is said to reflect a 'paradigmatic shift in theory, method and approach toward intervening with substance abuse' (O'Leary Tevyaw & Monti, 2004:64). HM may be more relevant to light users, to those with a short history of substance use, and to those who are not very motivated to stop using, as adolescents and young adults often are (Monti, Colby & O'Leary, 2001b). Promoting harm minimisation, instead of abstinence/cessation, might resonate well with adolescents who tend to view substance use as a normative phenomenon, and tend to reject and rebel against 'what grown-ups' expect of them. Data from international studies demonstrate the efficacy of brief HM interventions for adolescent drinking (eg, Baer et al, 2001; Monti et al, 1999) and smoking (eg, Colby et al, 1998). Findings from the South African interventions add to international data, providing some support for using HM approaches. Resnicow et al showed that both an LST and an HM intervention were effective, but differed according to populations: overall, black students seemed to respond better to HM messages, and coloured students to LST messages, and the HM intervention appeared to be more effective for boys. Wechsberg et al demonstrated the effectiveness of using a brief HM intervention for high-risk females, yet this intervention was not tested against a control group. Given the sound conceptual basis of HM, the international and local data supporting HM approaches, and the fewer resources required for their implementation, further testing of HM interventions may be warranted in South Africa.

Although both LST and HM approaches draw from sound psychological theoretical models, such as social learning theory (Bandura, 1977) and humanistic psychology (Rogers, 1975), these are not currently the main (or the only) theories used to study risk-taking. Specifically, risk-taking behaviours are being investigated via models of social cognition: for example, the health belief model (Rosenstock, 1966), protection motivation theory (Rogers, 1975), self-regulation theory (Leventhal, Safer & Panagis, 1983) and the theory of planned behaviour (Ajzen, 1991), which share the common assumption that people's perceptions, beliefs and cognitions lead to behaviour. Studying risk-taking behaviours with socio-cognitive models has shed light into which *specific* attitudes, beliefs, norms and significant referent influences impact risk behaviours for the populations at hand. For example, data drawn from studies that have used the theory of planned behaviour (Ajzen, 1991) to investigate predictors of university undergraduate binge drinking (Norman et al, 1998), demonstrated that frequent binge drinkers were less likely to believe that binge drinking was under their control, and more likely to cite a number of environmental factors that facilitated the behaviour. Marcoux and Shope (1997) applied the theory of planned behaviour to examine predictors of elementary and high school students' alcohol

consumption, and found that peer pressure and friends' experience with alcohol were the two most important variables in this model. Additionally, parental normative beliefs emerged as an important predictor of alcohol consumption. In South Africa, Morojele et al (2000) found that the theory of planned behaviour constructs were able to predict binge drinking intentions in female dropouts from three schools (Grade 12) in Cape Town, while pointing to possible 'cultural' influences. Each school comprised a differed racially stratified sample (white, coloured and black/Xhosa participants). Results differed according to racial composition: perceived behavioural control (ie, how easy it was for participants to engage in the behaviour) was established as an independent predictor of binge drinking in all schools; attitudes were a key predictor in the white and black/Xhosa schools; and subjective norms (ie, peer pressure) were an independent predictor in the coloured school only.

The point we are trying to make here is that, empirically, it makes more sense to base interventions on theoretical models created for, or directly relevant to, the study of health and risk activities, instead of basing interventions on broad psychological theories.

Another possible reason for the modest effectiveness of the reviewed interventions might be unsuccessful (or no) cultural adaptation. For example, Karnell et al and Cupp et al did not report a process of cultural implementation, and Smith et al placed too much emphasis on teacher perspective. Although teacher opinion is necessary when it comes to the practical aspects of delivering the intervention to their students, teachers are little more than observers of student life, often dismayed by student risk-taking experiences. Teachers may hold outdated or idealistic notions of what it means to be an adolescent, as well as unrealistic perceptions of actual student life. Therefore, using teachers and other adults (including experts) as main agents of programme development could potentially interfere with its efficacy. Enlisting students as experts is reportedly not only the best mechanism for achieving a culturally grounded curriculum (Holleran Steiker, 2006), but also studies have shown that the process of cultural adaptation/programme creation functions as an intervention in its own right (Holleran Steiker, 2008).

To sum up, it may be that conceptual, theoretical and methodological issues pertaining to adaptation processes contribute to diminished effectiveness of South African substance abuse interventions for young people.

Conclusion: suggestions for successful interventions

1. When programmes originate outside of South Africa, local researchers need to make sure that the imported intervention is of established effectiveness.
2. When importing interventions, cultural adaptations should use members of the target audience as primary information sources, whilst balancing for fidelity.
3. If a choice must be made between an LST and an HM approach, both strategies need to be tested against each other to assess best fit for the target population.
4. In general, moralistic judgments pertaining to the way of life of the target population need to be avoided.
5. Robust designs are the best (ie, RCTs), together with undertaking appropriate statistical analyses to account for the intra-class correlation coefficient (ICC).

Additionally, attrition needs to be reported, along with the ways it was dealt with (eg, by conducting an intention-to-treat analysis).

6. When applicable, the CONSORT Statement can be consulted as a means for enhancing the external and internal validity of the intervention.
7. Those who deliver the intervention must be adequately trained, both in theory and in practice.
8. Ideally, the intervention needs to be evaluated at all stages, from conception to outcome.
9. Given that knowledge and expertise exists, the creation of an original, authentic South African substance use intervention is warranted.
10. Because of scientific requirements of assessment, accountability and replication, final reports of the intervention must be clearly and analytically written, documenting all stages of intervention construction, implementation and evaluation.

References

Ajzen, I. (1991). The theory of planned behaviour. *Organizational Behavior and Human Decision*, 50(2):179–211.

Baer, J.S., Kivlahan, D.R., Blume, A.W., McKnight, P. & Marlatt, G.A. (2001). Brief intervention for heavy-drinking college students: 4-year follow-up and natural history. *American Journal of Public Health*, 91(8):1310–16.

Bandura, A. (1977). *Social Learning Theory*. Englewood Cliffs, N.J.: Prentice Hall.

Borsari, B. & Carey, K. (2000). Effects of a brief motivational intervention with college student drinkers. *Journal of Consulting and Clinical Psychology*, 68(4):728–33.

Botvin, G.J., Baker, E. & Dusenbury, L. (1995a). Long term follow-up results of a randomized drug abuse prevention trial. *Journal of the American Medical Association*, 273(14):1106–12.

Botvin, G.J., Baker, E., Dusenbury, L., Tortu, S. & Botvin, E.M. (1990b). Preventing adolescent drug abuse through a multimodal cognitive-behavioral approach: results of a 3-year study. *Journal of Consulting and Clinical Psychology*, 58(4):437–46.

Botvin, G.J., Baker, E., Filazzola, A. & Botvin, E.M. (1990). A cognitive-behavioral approach to substance abuse prevention: a one-year follow-up. *Addictive Behaviors*, 15(1):47–63.

Botvin, G.J. & Griffin, K.W. (2001). Life skills training: theory, methods, and effectiveness of a drug abuse prevention approach. In E.F. Wagner & H.B. Waldron (eds). *Innovations in Adolescent Substance Abuse Intervention.* New York: Elsevier Press.

Botvin, G.J., Schinke, S.P., Epstein, J.A., Diaz, T. & Botvin, E.M. (1995b). Effectiveness of culturally focused and generic skills training approaches to alcohol and drug abuse prevention among minority adolescents two-year follow-up results. *Psychology of Addictive Behaviours*, 9(3):183–94.

Caldwell, L.L. (2004). *TimeWise: Taking Charge of Free Time*. Scotts Valley, CA: ETR Associates.

Colby, S.M., Monti, P.M., Barnett, N.P., Rohsenow, D.J., Weissman, K., Spirito, A., Woolard, R.H. & Lewander, W. (1998). Brief motivational interviewing in a hospital setting for

adolescent smoking: a preliminary study. *Journal of Consulting and Clinical Psychology*, 66(3):574–78.

Cooper, M.L., Wood, P. & Orcutt, H.K. (1996). Covariation among adolescent problem behavior. ERIC No. ED 407 617.

Crosby, R.A., Diclemente, R.J., Wingood, G.M., Rose, E. & Lang, D. (2003). Correlates of continued risky sex among pregnant African-American teens – implications for STD prevention. *Sexually Transmitted Diseases*, 30(1):57–63.

Cupp, P.K., Zimmerman, R.S., Bhana, A., Feist-Price, S., Dekhtyar, O., Karnell, A. & Ramsoomar, L. (2008). Combining and adapting American school-based alcohol and HIV prevention programmes in South Africa: the HAPS project. *Vulnerable Children and Youth Studies*, 3(2):134–42.

Dane, A.V. & Schneider, B.H. (1998). Program integrity in primary and early secondary prevention: are implementation effects out of control? *Clinical Psychological Review*, 18(1):23–45.

Donaldson, S.I., Graham, J.W. & Hansen, W.B. (1994). Testing the generalizability of intervening mechanism theories: understanding the effects of adolescent drug use prevention interventions. *Journal of Behavior Medicine*, 17(2):195–216.

Donnor, A., Birkett, N. & Buck, C. (1990). Randomization by cluster sample size requirements and analysis. *American Journal of Epidemiology*, 114(6):906–14.

Donovan, J.E. & Jessor, R. (1985). Structure of problem behaviour in adolescence and young adulthood. *Journal of Consulting and Clinical Psychology*, 53(6):890–904.

Drucker, E. (1995). Harm reduction: a public health strategy. *Current Issues in Public Health*, 1: 64–70.

Dusenbury, L., Brannigan, R., Falco, M. & Hansen, W.B. (2003). A review of research on fidelity of implementation: implications for drug abuse prevention in school settings. *Health Education Research*, 18(2):237–56.

Egger, M., Jüni, P. & Bartlett, C. (2001). Value of flow diagrams in reports of randomized controlled trials. The CONSORT Group. *Journal of the American Medical Association*, 285(15):1996–99.

Elder, J., Sallis, J., Woodruff, S. & Wildey, M. (1993). Tobacco-refusal skills and tobacco use among high risk adolescents. *Journal of Behavior Medicine*, 16(6):629–42.

Flisher, A.J. & Chalton, D.O. (2001). Adolescent contraceptive non-use and covariation among risk behaviours. *Journal of Adolescent Health*, 28(3):235–41.

Flisher, A.J., Mathews, C., Mukoma, W. & Lombard, C.J. (2006). Secular trends in risk behaviour of Cape Town grade 8 students. *South African Medical Journal*, 96(9):982–87.

Flisher, A.J., Mukoma, M. & Louw, J. (2008). Evaluating adolescent sexual and reproductive health interventions in Southern and Eastern Africa. In K-I. Klepp, A.J. Flisher & S.F. Kaya (eds). *Promoting Adolescent Sexual and Reproductive Health in East & South Africa*. Cape Town: HSRC Press.

Flisher, A.J., Ziervogel, C.F., Chalton, D.O., Leger, P.H. & Robertson, B.A. (1996). Risk-taking behaviour of Cape Peninsula high-school students: Part IX. Evidence for a syndrome of adolescent risk behaviour. *South African Medical Journal*, 86(9):1090–93.

Foxcroft, D.R., Ireland, D., Lister-Sharp, D.J., Lowe, G. & Breen, R. (2003). Longer-term primary prevention for alcohol misuse in young people: a systematic review. *Addiction*, 98(4):397–411.

Hamilton, G., Cross, D., Resnicow, K. & Hall, M. (2005). A school-based harm minimization smoking intervention trial: outcome results. *Addiction*, 100(5):689–700.

Holleran Steiker, L.K. (2006). Consulting with the experts: utilizing adolescent input in substance use prevention efforts. *Sociological Perspective*, 28(1):53–66.

Holleran Steiker, L.K. (2008). Making drug and alcohol prevention relevant. Adapting evidence-based curricula to unique adolescent cultures. *Family Community Health*, 31(1):S52–S60.

Holleran Steiker, L.K., Sagun, D., Hopson, L.M. & Goldback, J. (2007). A community-based adaptation of an evidence based substance abuse prevention program: effectiveness for reducing alcohol use among adolescents. Poster presented at: Society for Prevention Research; 31 May 2007, Washington, DC.

Jernigan, D.H, 2001. *Global Status Report: Alcohol and Young People*. Geneva: World Health Organization.

Jessor, R. & Jessor, S.L. (1977). *Problem Behavior and Psychosocial Development: A Longitudinal Study of Youth*. New York: Academic Press.

Kaplan, H.B. (1980). *Deviant Behavior in Defense of Self*. New York: Academic Press.

Karnell, A.P., Cupp, P.K., Zimmerman, R.S., Feist-Price, S. & Bennie, T. (2006). Efficacy of an American alcohol and HIV prevention curriculum adapted for use in South Africa: results of a pilot study in five township schools. *AIDS Education and Prevention*, 18(4):295–310.

Kingree, J.B. & Betz, H. (2003). Risky sexual behavior in relation to marijuana and alcohol use among African-American, male adolescent detainees and their female partners. *Drug and Alcohol Dependence*, 72(2)197–203.

Leventhal, H., Safer, M.A. & Panagis, D.M. (1983). The impact of communications on the self-regulation of health beliefs, decisions, and behavior. *Health Education Quarterly*, 10(1):3–29.

Liang, H., Flisher, A.J. & Lombard, C.J. (2007). Bullying, violence, and risk behavior in South African school students. *Child Abuse & Neglect*, 31(2):161–71.

Leigh, B.C. (2002). Alcohol and condom use – a meta-analysis of event-level studies. *Sexually Transmitted Diseases*, 29(8):476–82.

Lyles, C.M., Kay, L.S., Crepaz, N., Herbst, J.H., Passin, W.F., Kim, A.S. Rama, S.M., Thadiparthi, S., DeLuca, J.B., Mullins, M.M.; HIV/AIDS Prevention Research Synthesis Team. (2007). Best-evidence interventions: findings from a systematic review of HIV behavioral interventions for US populations at high risk, 2000–2004. *American Journal of Public Health*, 97(1):133–43.

Marcoux, B.C. & Shope, J.T. (1997). Application of the theory of planned behavior to adolescent use and misuse of alcohol. *Health Education Research*, 12(3):323–31.

McGuire, W.J., 1968. The nature of attitudes and attitude change. In G. Lindzey & E. Aronson (eds). *Handbook of Social Psychology*. Reading, MA: Addison-Wesley; 136–314.

Miller, W.R. & Rollnick, S. (2002). *Motivational Interviewing: Preparing People for Change*. 2nd edition. New York: Guilford Press.

Moher, D., Schulz, K.F. & Altman, D.G. (2001). The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. The CONSORT group. *Journal of the American Medical Association*, 285(15):1987–91.

Monti, P.M., Abrams, D.B., Kadden, R.M. & Cooney, N.L. (1989). *Treating Alcohol Dependence: A Coping Skills Training Guide*. New York: Guilford Press.

Monti, P.M., Colby, S.M., Barnett, N.P., Spirito, A., Rohsenow, D.J., Myers, M., Woolard, R. & Lewander, W. (1999). Brief intervention for harm reduction with alcohol-positive older adolescents in a hospital emergency department. *Journal of Consulting and Clinical Psychology*, 67(6):989–94.

Monti, P.M., Colby, S.M. & O'Leary, T.A. (eds) (2001b). *Adolescents, Alcohol, and Substance Abuse: Reaching Teens Through Brief Interventions*. New York: Guilford Press.

Morojele, N.K., Parry, C.D.H., Ziervogel, C.F. & Robertson, B.A. (2000). Prediction of binge drinking intentions of female school leavers in Cape Town, South Africa, using the theory of planned behaviour. *Journal of Substance Use*, 5(3):240–51.

Mpofu, E., Caldwell, L., Smith, E., Flisher, A.J., Mathews, C., Wegner, L. & Vergnani, T. (2006). Rasch modeling of the structure of health risk behavior in South African adolescents. *Journal of Applied Measurement*, 7(3):323–34.

Nation, M., Crusto, C., Wandersman, A., Kumpher, K.L., Seybolt, D., Morrissey-Kane, E. & Davino, K. (2003). What works in prevention: principles of effective prevention programs. *American Psychologist*, 58(6/7):449–56.

Nestler, E.J. (2004). Historical review: molecular and cellular mechanisms of opiate and cocaine addiction. *Trends in Pharmacological Sciences*, 25(4):210–18.

Norman, P., Bennet, P. & Lewis, H. (1998). Understanding binge drinking among young people: an application of the theory of planned behaviour. *Health Education Research*, 13(2):163–69.

Oetting, E.R. & Beauvais, F. (1987). Peer cluster theory, socialization characteristics, and adolescent drug use: a path analysis. *Journal of Consulting & Clinical Psychology*, 34(2):205–13.

O'Leary Tevyaw, T. & Monti, P.M. (2004). Motivational enhancement and other brief interventions for adolescent substance abuse: foundations, applications and evaluations. *Addiction*, 99(2):63–75.

Palen, L., Smith, E.A., Flisher, A.J., Caldwell, L.L. & Mpofu, E. (2006). Substance use and sexual risk behavior among South African eighth grade students. *Journal of Adolescent Health*, 39(5):761–63.

Palinkas, L.A., Atkins, C.J., Miller, C. & Ferreira, D. (1996). Social skills training for drug prevention in high-risk female adolescents. *Prevention Medicine*, 25(6):692–701.

Parry, C.D.H., Myers, B., Morojele, N.K., Flisher, A.J., Bhana, A., Donson, H. & Plüddemann. (2004). Trends in adolescent alcohol and other drug use: findings from three sentinel sites in South Africa (1997–2001). *Journal of Adolescence*, 27(4):429–40.

Perry, C.L., Williams, C.L., Veblen-Mortenson, S., Toomey, T.L., Komro, K.A., Anstine, P.S., McGovern, P.G., Finnegan, J.R., Forster, J.L., Wagenaar, A.C. & Wolfson, M. (1996). Project Northland: outcomes of a community-wide alcohol use prevention program during early adolescence. *American Journal of Public Health*, 86(7):956–65.

Plüddemann, A., Parry, C.D.H., Cerff, P., Bhana, A., Sanca, P.E, Potgeiter, H., Gerber, W., Mohamed, F., Petersen, P. & Carney, T. (2007). The South African Community Epidemiology Network on Drug Use (SACENDU), phase 22. *SACENDU Research Brief*, l, 10(2).

Plüddemann, A., Parry, C.D.H., Cerff, P., Bhana, A., Sanca, P.E. & Potgieter, H. (2008). Monitoring alcohol and drug abuse trends in South Africa. *SACENDU Research Brief*, 11(1): 1–12.

Prochaska, J.O., DiClemente, C.C. & Norcross, J.C. (1992). In search of how people change: applications to addictive behaviors. *American Psychologist*, 47(9):1102–14.

Reddy, S.P., Panday, S., Swart, D., Jinabhai, C.C., Amosun, S.L., James, S. et al. (2003). *Umthenthe uhlaba usamila: The South African Youth Risk Behaviour Survey 2002*. Cape Town: South African Medical Research Council.

Rehm, J., Rehn, N., Room, R., Monteiro, M., Gmel, G., Jernigan, D. & Frick U. (2003). The global distribution of average volume of alcohol consumption and patterns of drinking. *European Addiction Research*, 9(4):147–56.

Resnicow, K., Cross, D. & Wynder, E. (1993). The Know Your Body program: a review of evaluation studies. *Bulletin of the New York Academy of Medicine*, 70(3):188–207.

Resnicow, K., Reddy, S.P., James, S., Omardien, R.G., Kambaran, N.S., Langner, H.G., Vaughan, R.D., Cross, D., Hamilton, G. & Tracy Nichols, T. (2008). Comparison of two school-based smoking prevention programs among South African high school students: results of a randomized trial. *Annals of Behavior Medicine*, 36(3):231–43.

Rhodes, T. & Cusick, L. (2002). Accounting for unprotected sex: stories of agency and acceptability. *Social Science & Medicine*, 55(2):211–26.

Ringwalt, C.L., Ennett, S., Johnson, R., Rohrbach, L.A., Simons-Rudolph, A., Vincus, A. & Thorne, J. (2003). Factors associated with fidelity to substance use prevention curriculum guides in the nation's middle schools. *Health Education & Behavior*, 30(3):375–91.

Rogers, C.R. (1957). The necessary and sufficient conditions of therapeutic personality change. *Journal of Consulting Psychology*, 21(2):95–103.

Rogers, R.W. (1975). A protection motivation theory of fear appeals and attitude change. *Journal of Psychology*, 91(1):93–114.

Rosenstock, I.M. (1966). Why people use health services. *Milbank Memorial Fund Quarterly*, 44(3):94–124.

Shapiro, T. (1985). Adolescent language: its use for diagnosis, group identity, values, and treatment. *Adolescent Psychology*, 12:297–311.

Sheeran, P., Abraham, C. & Orbell, S. (1999). Psychosocial correlates of heterosexual condom use: a meta-analysis. *Psychological Bulletin*, 125(1):90–132.

Smith, E.A., Palen, L.A., Caldwell, L.L., Flisher, A.J., Graham, J.W., Mathews, C., Wegner, L. & Vergnani, T. (2008). Substance use and sexual risk prevention in Cape Town, South Africa: an evaluation of the HealthWise Program. *Prevention Science*, 9(4):311–21.

Taylor, M., Dlamini, S.B., Kagoro, H., Jinabhai, C.C. & De Vries, H. (2003). Understanding high school students' risk behaviors to help reduce the HIV/AIDS epidemic in KwaZulu-Natal, South Africa. *The Journal of School Health*, 73(3):97–100.

Tomkins, D.M. & Sellers, E.M. (2001). Addiction and the brain: the role of neurotransmitters in the cause and treatment of drug dependence. *Canadian Medical Journal*, 164(6):817–21.

Turner, C.F., Miller, H.G. & Moses, L.E. (eds) (1989). *AIDS, Sexual Behaviour, and Intravenous Drug Use*. Washington, DC: National Academy Press.

Wechsberg, W.M., Luseno, W.K., Karg, R.S., Siobhan Young, S., Rodman, N., Myers, B. & Parry, C.D.H. (2008). Alcohol, cannabis, and methamphetamine use and other risk behaviours among Black and Coloured South African women: a small randomized trial in the Western Cape. *International Journal of Drug Policy*, 19(2):130–39.

Wegner, L., Flisher, A.J., Caldwell, L.L., Vergnani, T. & Smith, E.A. (2008). HealthWise South Africa: cultural adaptation of a school-based risk prevention programme. *Health Education Research*, 23(6):1085–96.

15 Interpersonal violence in South Africa and substance misuse: connections and approaches to prevention

Catherine L. Ward

Introduction

As well as having one of the highest rates of substance abuse in the world, South Africa has one of the highest recorded rates of interpersonal violence in the world (Norman, Matzopoulos, Groenewald & Bradshaw, 2007). This chapter uses a control theory perspective (Gottfredson & Hirschi, 1990; Le Blanc, 1997; Catalano & Hawkins, 1996) to trace the origins of both problems to the impact of the nation's colonial and apartheid history on families, education and employment, and the differential access to resources for different race groups that this history created. The chapter focuses chiefly on youth development, for two reasons: in terms of interpersonal violence, it is young people (chiefly young men) who are most at risk (Norman et al, 2007); and a focus on youth development lends itself most naturally to a focus on prevention, which this chapter will also attempt to address briefly.

Violence and substance misuse in South Africa

The national homicide rate (64.8 per 100 000 in the year 2000) places South Africa among the most violent places in the world (Norman et al, 2007). Homicide is the second leading cause of death after HIV/AIDS (Bradshaw et al, 2003). Non-fatal injuries also occur at very high rates, compared with other countries where recorded rates are available (Norman et al, 2007). It is clear that one of the major drivers of this high rate of mortality and injury is alcohol use (although other intoxicating substances are also implicated). A series of studies of patients presenting to trauma units in major centres across the country consistently finds that more than half of patients present with injuries resulting from interpersonal violence, and those whose injuries have been sustained as a result of violence are more likely to test positive for alcohol than those whose injuries were sustained in an unintentional manner. Furthermore, the most frequently used substances in this group were alcohol, followed by cannabis and (in Cape Town) a combination of cannabis and methaqualone (Plüddemann, Parry, Donson & Sukhai, 2004; Bowley et al, 2004; Peden, Van der Spuy, Smith & Bautz, 2000; Parry et al, 2005; Parry, Tibbs, Van der Spuy & Cummins, 1996). Alcohol is also the most common primary substance of abuse that presents at treatment sites across the country (Plüddemann et al, 2009).

The apartheid connection

A uniquely South African twist to this story comes with the hints from epidemiological studies that the use of most substances, including alcohol, differs by race and class (see Chapter 1 for a full discussion). For instance, in a national study, white men were most likely, and Asian women least likely, to drink alcohol. Alcohol problems were associated with lower socio-economic status, no school education (in women) and being over the age of 25 (Parry et al, 2005). A study of patients accessing community health centres in Cape Town for primary care found that black women were least at risk for using all substances, while the use of drugs other than alcohol was particularly associated with coloured men and women (Ward et al, 2008). Other indicators of these demographic differences include the high rates of fetal alcohol syndrome in wine-growing areas (May et al, 2000), where farm workers, usually coloured labourers in these areas, were historically paid by the 'dop' system – crude wine from the farm to start and end the day, a habit that has influenced drinking patterns among agricultural labourers today (London, 1982). Race and class (in the sense of ability to pay) also influence who presents for treatment, and there are also possible race and gender effects at play in terms of primary drug of choice among patients presenting at treatment centres (Plüddemann et al, 2009).

Of course, race and class are not intrinsically linked to substance misuse. They are merely signifiers for who has access to which resources – perhaps most notably, who has access to the protections conferred by education, employment and treatment, and access to what quality of these resources. Current studies show that education and employment are both associated with what substances one uses and the extent of that use or misuse (see, for instance, Parry et al, 2005; Ward et al, 2008; Chapter 1, this volume), a view which is consistent with control theories of risk behaviours (both substance misuse and violence, as well as other risk behaviours such as delinquency generally; see Gottfredson & Hirschi, 1990; Le Blanc, 1997; Catalano & Hawkins, 1996). Current studies also show that different races and classes have different access to treatment (Myers, Louw & Fakier, 2008; Plüddemann et al, 2009).

Social controls and the effects of colonialism and apartheid

Control theory perspectives typically focus on adolescent development, asserting that the ability of young people to develop prosocial behaviours (rather than antisocial ones) depends on the extent to which adolescents are able to internalise controls, or prosocial values, attitudes and behaviours, through socialisation processes in important contexts, particularly the family, the school and the community (Gottfredson & Hirschi, 1990; Le Blanc, 1997; Catalano & Hawkins, 1996). In this sense, control theory stands outside the debate about choice versus disease that is described, for example, in Chapter 11 of this volume: instead of considering individual choice or illness, control theory perspectives ask about whether the conditions present during child and adolescent development made it more likely that someone would internalise prosocial or antisocial values and behaviour.

Coovadia, Jewkes, Barron, Sanders & McIntyre (2009) trace the colonial and apartheid history of South Africa, which is summarised briefly here as background. The first white settlers came to South Africa in 1652 to found a refreshment station for the Dutch East India

Company at the Cape of Good Hope. The Cape at that time was occupied by the indigenous San and Khoikhoi peoples, who were dispossessed of their lands by the white settlers and either forced to work on settler farms or driven off. From 1654, slaves were imported into the Cape to work on the farms, from West Africa, Indonesia, India, Mozambique and Madagascar. The descendants of these slaves and farm workers were to be some of the people classified coloured or Asian (Indian) under apartheid. In 1806 Britain took over rule of the Cape Colony from the Dutch East India Company. Over the following century, migration and military expansion from the Cape Colony saw the occupation of what is today South Africa. In the process, several other indigenous African tribes, such as the amaXhosa and the amaZulu, were encountered and subdued through the military might of the colonial power. In 1910, the Union of South Africa brought together the two Afrikaner republics (the Transvaal and the Orange Free State) and the two British colonies (the Cape and Natal) as provinces within a single state, which then became a dominion within the British Empire. The Union had been opposed by the African National Congress, which had been formed in 1912, because it denied representation to the black majority. Apartheid was introduced formally in 1948, when the National Party came to power. Resistance to apartheid increased sharply from 1960 onwards and eventually led to the dismantling of apartheid and to the first democratic elections in 1994.

This necessarily brief outline of South Africa's political history serves as a prelude to a more detailed discussion of how access to the resources of family, education and work has become organised along race and class lines that still influence such access today. In addition, this history has also influenced access to alcohol. As Mager (2004) describes, grapes had been grown for alcohol since the earliest days of white settlement in the Cape (mid-1600s), and by the 1800s a liquor industry was thriving. This led to a bifurcation in the way alcohol was viewed, and hence to a bifurcation in the way it was handled: the sale of alcohol was good for the economy of the young colony and therefore to be promoted, but while white drunkenness could be tolerated, African drunkenness was to be feared, a view that was fuelled partly by racial phobia, but also partly by economic concerns, since an effective workforce needed to be sober (Mager, 2004). A commission of inquiry was instituted to address this problem in the late 1800s, and the chosen solution was selective prohibition: in what is now the Western Cape, a steady flow of alcohol was to be maintained to coloured farm labourers by means of the 'dop' system – thus effectively creating a dependency on the farmer – but otherwise labourers for farms and mines were to be maintained relatively sober so that they could continue to be productive. Prohibition for whites, however, was not considered (Mager, 2004). Selective prohibition was only repealed in 1961 (Mager, 2008).

Later, under apartheid, several government initiatives also attempted to control access to alcohol. For instance, although home-brewed beers had long been part of traditional life in many indigenous groups, government assumed control of the manufacture and sale of these with the Native Urban Areas Act of 1923 and the Sorghum Beer Act No. 63 of 1962 (Mager, 2008). Together with a prohibition on people of colour setting up commercial enterprises, and the general prohibition on sales of alcohol to people of colour, this led both to a proliferation of shebeens (illegal liquor outlets) and to the promotion of South African Breweries' production of sorghum beer (Mager, 2008). However, after the 1976 student uprisings, clear beer – produced by commercial liquor producers – suddenly began

to replace traditional beer in popularity, as young drinkers began to introduce new drinking rituals as part of the struggle against apartheid, and the commercial producers capitalised on this with novel, struggle-oriented marketing techniques aimed at the township markets (Mager, 2004). Since market growth has been in this illicit industry rather than in legal markets, it has been in the interest of South African Breweries to keep it supplied in order to hold onto the market share (two-thirds of the South African beer market), and to keep a strategy of maintaining low prices in the townships that are affordable to the low-wage earners in that market (Mager, 2008).

Clearly, therefore, access to alcohol at least has been (and still is) structured along race and class lines. However, habits of risky substance misuse, and how this develops along race and class lines, may also be understood from a control theory perspective, if one considers the influence of colonialism and apartheid on the key socialising arenas of the family, the community and the school. Control theories, in essence, hold that when young people have warm relationships with parents (who are able to monitor their whereabouts and their relationships with their friends, and enforce household rules without resorting to rigid or harsh punishment); when they have friends who are not themselves delinquent; when they attend functioning schools to which they have formed an attachment and which offer them a hope for the future after school; and when their broader communities work together with these smaller social institutions to reinforce social norms such as working for a living, then it is less likely that substance use (or violence, or criminal activities, or risky sex) will be viewed as options by young people (Gottfredson & Hirschi, 1990; Le Blanc, 1997; Catalano & Hawkins, 1996). It is in their effects on the school, the family and the community that colonialism and apartheid also set the scene for widespread substance misuse and violence.

Education, apartheid and substance misuse

In terms of education, perhaps the earliest direct association between schooling and substances is noted in Jan van Riebeeck's diary on 17 April 1658 (six years after he arrived at the Cape):

> Began holding school for young slaves … To stimulate the slaves' attention while at school, and to induce them to learn the Christian prayer, they were promised each a glass of brandy and two inches of tobacco when they finish their task. (Quoted in Christie, 1985:32, citing Horrell, 1970:3)

However, most of the influence of colonialism on substance use through schooling was not so direct, but rather via its segregation of the races and the institution of inferior education for 'non-European' races.

Very little in the way of schooling was available for children of any race group in the early centuries of the colony (Christie, 1985). What was available typically had religious content and purposes, and was not always segregated. However, this began to change when the British assumed control of the Cape Colony, as they paid more attention to education than the Dutch, and by 1839 they had set up a Department of Education and were subsidising schools. Primary education was made free, but secondary education was not. And alongside

the free schools, there were private schools that were available only to the wealthy. However, these changes had effect chiefly in towns; many rural children (including white children) received little or no education.

Two important laws were passed during this period which were to have effects on schooling. In 1828, Ordinance 50 in the Cape gave equal rights to 'free persons of colour'; they were thus no longer tied to agricultural work but could migrate to the towns (Pinnock, 1982). In 1833, across the British Empire, all slaves were freed, and of course Ordinance 50 applied to them, too. The ultimate effect of this was that white farmers could no longer rely on slave labour to work their land, and by 1900, in Cape Town at least, there were large squatter camps and overcrowded tenements (Pinnock, 1982). Christie (1985) argues that schooling was then used to instil 'social discipline', especially among 'coloured' people, who were to be prepared via schooling to become wage labourers. She goes on to point out that this schooling may have made elementary education available to some 'coloured' people, but by no means all, and certainly secondary education remained beyond their financial grasp. Secondary and higher education remained the domain of the privileged, and so education introduced a class differential (Christie, 1985).

Similarly, education for African people was provided by mission schools, often with the explicit aim of making them a part of the colony (rather than 'dangerous barbarians' living on the colony's borders) – but as unskilled labourers, not as skilled workers. By the end of the 1800s there were a few Africans who were sufficiently well educated to have earned the vote, but they were distinctly in the minority.

These patterns of unequal schooling were echoed in the Transvaal, Natal and the Orange Free State. Wealthy children received more schooling than the poor, and Africans were educated to become labourers. As minerals (chiefly gold and diamonds) were discovered and the mining industry established, these differences in labour became even more entrenched along racial lines: white workers did skilled jobs, were paid more, and could unionise. Almost all black workers did unskilled work, were paid less, and could not unionise; their movements were also controlled by pass laws, and so they could not work where and when they pleased. At first these situations were informal, but by 1923 they were instantiated in law.

The development of mining drove a concomitant need for skilled labour, and hence drove an increased push for free education. The British administration had taken over education in the Transvaal and the Orange Free State after the Anglo-Boer War, and in 1902 in the Transvaal free primary education was made compulsory for all whites. This was followed shortly by similar ordinances in all provinces, and then the ages of attendance were made compulsory from 7 to 14, and then 7 to 16 years. However, education was not made compulsory for Africans, although increased funding was given to mission schools.

During the 1940s, industrialisation continued apace, driven by the Second World War and the need to ensure that the country could survive even if all supply lines were cut off. Migration to towns continued to increase, as they appeared to offer the best chance of survival. In 1948, the National Party was elected to power, and began to institute the apartheid system on the base that had already been established. In 1953, the Bantu Education Act was passed, which required all schools for Africans to be registered with the government, and which therefore effectively closed most mission schools. Acts governing

coloured education (1963), Indian education (1965) and white education (1967) were then passed. The net effect of these acts was to entrench class inequalities in education.

Although these acts have been repealed and there is now one National Department of Education for all children, the effects of the apartheid system continue to be felt in South African schools. Inherited inequalities in schools persist alongside the inequalities of residential neighbourhood, and differential fees and fund-raising capacities across neighbourhoods are among the mechanisms that continue to drive inequalities (Lemon & Battersby-Lennard, 2009). There are also differences in learner-educator ratios and in educational quality across white and black schools (Yamauchi, 2005), as well as poorer facilities and human capital in black schools (Fiske & Ladd, 2006).

Perhaps the ultimate failure of schooling for young people of colour is that, at each point in South Africa's history, as now, it has failed to provide a clear connection between education and the job world (Mokwena, 1991). This is borne out by a comparison between success at the senior certificate (school-leaving) examination, and employment rates. Since 2001, the pass rate in the senior certificate examination has varied between 61.7% and 73.3%, but unemployment (the percentage of young people who were actively looking for work) in the age range 15–24 years over the same period has varied between 46.1% and 59.1% (Presidency, 2009). Many young people have therefore left school in the hopes of finding a job, but have not been successful.

The education that today's young people have inherited from the colonial and apartheid systems is thus both poorly resourced and not very likely to lead to work. This undermines its effectiveness as a socialising instrument. There is little point in attaching to, and internalising the values of, an institution that is as weak as the schools that were historically for children of colour. One indicator of this is the high rate of dropout (see, for instance, Wegner, Flisher, Chikobvu, Lombard, & King, 2008), which carries with it an increased risk for substance use (Townsend, Flisher & King, 2007). Dropout and substance use also carry with them an increased risk of delinquency and crime (Ellickson, Saner & McGuigan, 1997), probably because young people with relatively less education have relatively less likelihood of entering the legitimate job market, and hence relatively fewer means of legitimately accessing material goods (or of coming by the means to pay for their drug of choice). They are therefore at an increased risk of turning to crime as a means to an end.

Families, apartheid and substance misuse

Colonialism and apartheid affected families, also a key socialising influence for young people. As with their effect on education, this history, too, is intertwined with the economic growth of the country. With mining and associated manufacturing driving the economy, the demand for cheap (black male) labour grew apace, and a combination of legislation, taxes and restrictions on access to land combined to undermine what had been a thriving rural black agricultural economy, to drive black men into mine labour (Coovadia et al, 2009). Coovadia et al (2009) note that there were 10 000 miners in 1889, and that this had doubled by 1910, and doubled again to 40 000 by 1940. Men began to migrate to urban areas in order to find work in the mines. Women and children, however, tended to remain in rural areas, as there were fewer work opportunities for women in the towns.

After 1948, when the National Party came to power, the system was solidified when the former rural land reserves were designated as Bantustans, or black homelands, and black people were recognised only as citizens of these new 'states', rather than as citizens of South Africa. However, the only available employment was in the cities, which could be accessed by those who carried the appropriate passes. The Bantustans therefore were large, poverty-stricken areas inhabited largely by unemployed women, children, the elderly and the infirm, while able-bodied men were away at work in the cities (Coovadia et al, 2009). The very structure of black families was undermined by the economic structure of the country.

Many coloured families had always lived in the cities, initially as slaves and then as free workers. They were, however, by no means immune to the effects of colonialism, apartheid and their relationship with economics. One well-documented area that gives insight into the effects on both families and a community is District Six in Cape Town. Pinnock (1984) documents how, after the First World War, District Six started to become a place where working class people could live and scratch out a living in the nearby city. Often these were coloured families, but the area also included black, Jewish, Indian and other recent immigrants to Cape Town (Hart, 1990). According to Pinnock (1984), it had a population of 22 440 in 1936; by 1940 this was around 40 000, as migration into the city continued. Under these conditions, every available piece of housing was overcrowded, and waiting lists for accommodation were long. On the one hand, and perhaps inevitably, this level of poverty and overcrowding was accompanied by problems: shebeens and gambling-houses sprang up, and street gangs formed. The Globe Group, a group of older shopkeepers, exerted some control over the street gangs in the 1940s, but the gangs also began to demand protection money from those who ran businesses in their territory, were for hire as a political hit-force, and ran their own shebeens and gambling dens (Pinnock, 1984). As Hart (1990) notes, this gang activity was a form of internal policing rather than a threat to the ordinary residents of District Six.

However, despite these problems of the urban slum, literary and oral evidence attest to a thriving community in District Six with a tremendous sense of place and of belonging (Hart, 1990; Nasson, 1990; Dudley, 1990). Part of what seems to have played a role in creating this fabric was a density of places of worship and small shops where impoverished families could buy small amounts of what was needed – a single potato, a few spoons of jam – or buy on credit, because they were known (Nasson, 1990). What must crucially be recognised, too, is that jobs were available to this poor and poorly skilled community in the docks and railways, the building trade, fishing and food and clothing production (Bickford-Smith, 1990). These sectors had grown in the years following the Second World War (Pinnock, 1984), and all were geographically within a short distance of District Six, and therefore within reach of its residents.

This was all threatened with the institution of apartheid and the Group Areas Act of 1950, which designated certain areas of the country for particular race groups. In February 1966 the larger part of District Six was formally proclaimed a white area under the Group Areas Act; it had taken that long because the Cape Town City Council was in opposition to the national government over declaring the area white (Hart, 1990). However, from 11 February 1966, the 33 500 residents who had been officially enumerated in the most

recent census (and who were identified as 'non-White') were given one year to prepare for removal to a new township. The national government then granted funds to the city to build housing schemes at Rylands Estate, Belhar and Hanover Park. Estimates of those actually moved vary from 55 000 to 60 000. The discrepancy between these estimates and the official census is explained by the high levels of immigration to the area and the high levels of so-called 'illegal dwelling' (Hart, 1990).

The effects of these removals, for those who did get new housing, were several. First, many were denied compensation for payments on what was essentially a hire-purchase scheme towards buying their houses. Those who were in arrears on their rental were denied rights to alternative housing. And those who had invested in maintenance of houses they had rented were denied any compensation (Hart, 1990). Alternative housing was often less than adequate, and particularly fell short in terms of the density of shops and places of worship that District Six had provided. Many other community services were also less than adequate, even compared with District Six (Hart, 1990). Significantly, however, removal to the new townships moved people long commuting distances from their sources of income, and, frequently, raised their rental (Hart, 1990). It is in this economic separation, and also in the breakdown of informal community ties that provide controls for young people and their families, that today's coloured gangs began to form.

Pinnock (1984:56) quotes an interview conducted by Western (1981), in which Western's respondent gives a wonderful example of the informal social controls which had prevailed among coloured families in Mowbray, prior to their removal under apartheid:

> When I was 15 or 16 if we did anything rude, offhanded, in the street – like going to bars or smoking or taking a dame out – you'd get a pak [slap] at night at home; they [parents] knew about it right away … It was the old men who used to stand at the corners chatting or sit on the stoeps; they'd pretend to be reading the Koran or a comic or playing *karem* or whatever, but out of the corner of their eye they were really watching you.

This was the social support that helped working class families to parent, and that kept their children out of trouble. However, with the removals to the new townships, these networks were broken, as individual families (and sometimes pieces of families) were moved to different places, rather than neighbourhoods being moved together (Pinnock, 1984). The change was further marked by an increase in single motherhood among coloured women, and a lack of access to extended family care for children, in the generation that first had their children in the townships – a dramatic change from the way in which these women had themselves been parented, and an indicator of how families ties had been disrupted (Pinnock, 1984).

Similar changes would of course have been experienced by black families who had been forced to live in urban 'locations' by the Urban Areas Act of 1923, by black families forcibly moved out of District Six into 'black group areas', and by coloured families moved out of other areas into 'coloured group areas'. District Six is just one particularly well-documented example.

Another influence on family life in South Africa, particularly on families of colour, was the political struggle, which during the 1980s became more youth-based. Following the

1976 school uprising in Soweto, young people moved more and more into the vanguard of the anti-apartheid struggle, and school boycotts became more and more frequent. Although the authority of the state was challenged in the streets and at school, this often led to intergenerational conflict at home, and families were weakened as young people also challenged the authority of their parents (Mokwena, 1991). Mokwena (1991) thus suggests that the political culture of the 1980s became the dominant socialising force for many young people, who, without the stabilising forces of family or school, began to slide into the life of the streets where they may easily have been introduced to a life of crime.

Some indicators of problems in family life today include apparently high rates of child maltreatment across the country (Dawes & Ward, 2008; Richter & Dawes, 2008) and high rates of intimate partner violence. In a recent nationally representative study of youth victimisation, conducted among young people aged 12–22, 21.8% reported witnessing violent disputes between members of their families (Leoschut & Burton, 2006). These are often serious altercations: in 39.8% of these disputes, a weapon was used, and in 27.6%, injuries were sustained (Leoschut & Burton, 2006). Other indicators of problems in families, from the same survey, are that 8.3% of adult members of households were reported to have used illicit drugs, and 2.1% were reported to have dealt in drugs; a far higher percentage (10.5%) were reported to have done something that broke the law (Leoschut & Burton, 2006). Coloured participants were more likely to report witnessing violence at home, followed by black and then Indian participants (Leoschut & Burton, 2006), indicating that much of the fracturing of families and communities that was introduced by colonialism and apartheid continues to be experienced by today's families.

The net result of the weakening of the family, the school and the community as socialising influences (as prosocial influences, that is), and the removal of the opportunity for meaningful work (in some cases, even work of any sort), has been to increase risk for crime. One form that this has taken is the formation of gangs in township areas. Pinnock (1984) suggests that gangs in Hanover Park are an inevitable consequence of the removal of families from District Six to Hanover Park, because this removal broke the ties of community and family, and removed access to income. Steinberg (2004) traces how gangs developed around the mining industry in Johannesburg: young black men, disaffected from the notion of low-wage labour as the only option open to them, formed gangs and began robbing miners. This eventually led to the formation of the 'numbers' gangs that persist through all the country's prisons today, and which have links to gangs outside of prison (Steinberg, 2004). Mokwena (1991) suggests that gangs in Soweto emerged in waves: first in response to mining, as Steinberg (2004) suggests; then in the 1950s in response to the establishment of the urban townships; then, after a period of relative control in the 1960s (marked by economic growth and the institution of Bantu education), there was another wave of gangs in the 1970s in response to the economic recession of that decade; and finally, gangs emerged again partly as a consequence of the weakening of social restraint during the political resistance to apartheid of the 1980s. One of the indicators of the extent of the breakdown of family, school and community is the endurance of high levels of gang involvement. Estimates from the 1990s suggested that there were then 130 gangs in Cape Town alone, with 100 000 members (Standing, 2005).

Gangs and substances

There are, of course, clear direct relationships between gangs and drugs. Pinnock (1984) notes that a predominant gang ritual for Cape Town gangs since the mid-1970s had been the smoking of a 'white pipe', the smoking of cannabis and methaqualone (known colloquially as dagga and Mandrax, respectively) together in a broken bottle. Otherwise, however, it is only recently that the connection between gangs and drugs has explicitly been noted. Young people who lived in Cape Town communities noted that gangs were centrally involved in the drug trade, and that substance misuse was a frequent route into the gang for young addicts. In order to fund their addiction, they might begin running drugs for the gang, and this might eventually lead to full membership (Ward & Bakhuis, 2009). The establishment of democracy in South Africa has facilitated drug trading for gangs, since it has led to weakened border controls, and allowed gangs within South Africa to connect with organised crime groups outside the country, who are, among other factors, literally trading on South Africa's convenient geographical position on international drug routes (Louw, 1997). One of the connections between drugs and violence, then, is not only the direct connection between intoxication and individual acts of violence, but turf wars between rival gangs over drug sales areas (Legget, 2005).

Families, schools and communities today

Apartheid and colonialism thus created conditions in which families, schools and communities were weakened, and both joblessness and the inability to seek gainful work reached high levels. Although South Africa has had a democratic government since 1994, the period has proved too short a time to reverse these trends. Many people of colour still live in the townships to which apartheid relegated them, and these areas continue to be under-served (for instance, see Nleya, 2008). One of the continued features of townships is the many shebeens, which may have originated during prohibition (Mager, 2004), but which today may be licensed or unlicensed. They continue to be at high density in township areas, and are frequently the site of alcohol-fuelled violence, as noted in a study of Cape Peninsula townships (Bray, Gooskens, Kahn, Moses & Seekings, 2010). Often, these provide the sole income for a family, and they are also a high revenue earner for South African Breweries (Mager, 2008). Drug houses, where drugs other than alcohol are sold, are also found with high frequency in townships (Bray et al, 2010; Ward & Bakhuis, 2009). These problems – high numbers of illicit points of sale for alchol and drugs, particularly when associated with violence – contribute to undermining community cohesion in the areas in which they exist.

It bears mention that violence and gangs are not the only problems associated with drugs and alcohol. Shebeens are frequently the sites for transactional and risky sex that may fuel the HIV epidemic (Morojele et al, 2006; Kalichman, Simbayi, Vermaak, Jooste & Cain, 2008). Of course, alcohol- and drug-fuelled sexual interactions in more private spheres also tend to increase HIV risk. For instance, high school students who had used methamphetamine were found to be more likely to have engaged in risky sexual practices (Plüddemann, Flisher, Mathews, Carney & Lombard, 2008). Alcohol use is generally a risk for high-risk sexual behaviour, particularly among men (Kalichman, Simbayi, Kaufman, Cain & Jooste, 2007), and substance use generally is related to a range of HIV risk behaviours in 18–24-year-olds

(Ward et al, 2005). Certain gangs also incorporate sexual violence risk-taking as part of their rituals. For instance, the Jackrollers of Soweto abducted and raped women, an act that became popularly known as 'jackrolling' (Mokwena, 1991). Although this is perhaps the most explicit form of sexual violence noted in the gang literature, other studies note women's fear of gangs, suggesting that girls who have gangster boyfriends are motivated to do so partly for protection, although also for the material goods that that these young men can supply (Ward & Bakhuis, 2009). Conversely, young men may be motivated to join gangs because they perceive that access to material goods may help them attract women (Ward & Bakhuis, 2009).

Aside from these continued effects at the family, school and community level, there are also continued influences at the level of the economy. Unemployment continues at a high rate: the overall rate in June 2009, by the 'broad' definition (those who were available to work, regardless of active work-seeking), was 32.5% (Presidency, 2009). An additional problematic indicator is that the Gini coefficient, the measure of the gap between rich and poor, seems to have grown as the economy has expanded. In 1995, it was 0.640, but in 2008 was 0.679 (Presidency, 2009). These problems will fuel the disconnect between school and work. In addition, with the discrepancy between rich and poor seems to have gone a longing for material goods that fuels crime and the attraction of gangs, where senior gangsters live obviously materially well-off lives, and offer material attractions to poor youngsters (Ward & Bakhuis, 2009).

Alcohol and drug misuse are therefore intrinsically interconnected with other social problems in South Africa, including gangs, violence and risky sexual behaviour. Among the causes of these problems are breakdowns in family life, in schooling, in community cohesion, and a low employment rate and the loss of the resultant connection between school and work. Each of these factors has been deeply influenced by the country's history of colonialism and apartheid.

Prevention: connections between substance misuse and violence

When young people who lived in communities with high levels of gang activity were asked what should be done about the gang problem, they made very few suggestions about tertiary prevention (dealing with existing gang members), none about secondary prevention (targeting populations at risk), but rather directed the bulk of their suggestions towards primary prevention – towards developing social structures that would enable a wide range of positive youth development (Ward & Bakhuis, 2009). Clearly, this is where our energies should be directed in the long term, if we wish to undo the legacy of colonialism and apartheid, and build a society in which communities, families, schools – and the people who depend on them – can flourish.

This is not to say that tertiary prevention should be neglected. In addition, in considering the intertwined problems of substance misuse and violence, interventions that address one or the other, or both, should be considered. For instance, an intervention to reduce substance misuse is likely to reduce violence (Ellickson et al, 1997), while an intervention to assist a gang member to withdraw from the gang might need to include substance abuse treatment (Josi & Sechrest, 1999; Schram & Gaines, 2005). At the moment, however, since

even access to good treatment is fractured along race and class lines (Myers et al, 2008), this is a state of affairs that needs redress.

It is worth mentioning that of course there are a few prevention programmes with a sound evidence base that is specific to South Africa, and those that are specific to substance misuse are reviewed elsewhere in this book. However, the approach here has been twofold: firstly, to suggest that programmes should target the identified risk factors; if this does not occur, the programme is not likely to have any effect, regardless of its effect in any other context. Secondly, it should be noted that risk factors for violent behaviour, for delinquency, for gang membership and for substance misuse among young people are non-specific: the same risks (breakdowns of family, school and community contexts) apply to all three problems. With that in mind, a few programmes have been suggested to illustrate the concepts of (1) an evidence base, (2) targeting risk factors and (3) drawing on a wider range of literature than may have been drawn on in other chapters in this book, which are likely to draw more narrowly on the substance misuse literature.

In terms of intervening with gangs, for instance, traditional gang literature suggests four different classes of approach (Spergel, 1995): prevention (preventing young people from getting involved in the gang in the first place), disengagement (helping gang members to withdraw), suppression (suppressing the activities of existing gangs, through policing and justice system interventions) and 'mixed models' (combinations of the previous three). Typically, however, those models that have been tested show very little ability to impact the existence of the gang itself, since gangs arise from community and economic conditions rather than from individual malaise (Hagedorn, personal communication, 2009). What must be recognised, therefore, is that – like substance abuse treatment – these models for gang intervention may have some effect for individuals, but will have little or (probably) no effect on communities. This is a general principle that needs to be borne in mind when thinking about programmes in this area: those that target individuals may help those individuals, but other individuals are likely to develop the same problems if the causal social structures are not altered.

That said, there are a number of prevention programmes with an evidence base for the prevention of delinquency and substance misuse that are worth mentioning, provided one keeps this individual perspective in mind. These include nurse home visitation programmes for mothers and young infants (Olds, Hill & Rumsey, 1998); the Olweus Bully programme, which is a whole-school approach to preventing bullying (Limber, 2006); and the Montreal Preventive Treatment Programme, which provides parent training to parents of at-risk boys, who also receive social skills training (Tremblay, Mâsse, Pagani, & Vitaro, 1996). These programmes effectively target risk factors identified here: they increase parent-child bonding and the skills with which parents parent, or they increase the attractiveness of the school environment. Aside from these three programmes, there is another type of programme that may be worth mentioning even though it has not yet been evaluated, because it aims to improve the education-work connection (Cooper & Ward, forthcoming). One example of such a programme is DIGEEX (Direccion General de Educacion Extra-Escolar; USAID, 2006), which aims to provide education that is directly linked to employment opportunities in a particular community. For example, in a community where the economy is driven by the textile market, training would involve

textile-industry-relevant skills and problem-solving tailored to the textile industry. This type of programme may be worth exploring even though it has, as yet, no evidence base, precisely because it targets a risk factor.

Disengagement programmes, on the other hand, attempt to wean current gang members away from the gang. In general, these are of two types: one tries to 'treat' the individual gang members' problems, while the other emphasises that those who leave the gang lifestyle must have a means of making a living (Cooper & Ward, forthcoming). Like prevention programmes, effective programmes in both groups attempt to address risk factors. An example of the first kind is a parole programme called Operation New Hope, in which young people who are about to leave prison on parole attend 13 weekly sessions of life skills training, which address topics such as drug use, emotion regulation, employment and education opportunities. Among other outcomes, programme participants were significantly less likely to use illicit drugs and to have contact with former fellow gang members, and were significantly more likely to find employment (Josi & Sechrest, 1999). An example of the latter is a programme from Medellín, Colombia, which offers long-term employment programmes if gang members withdraw from their gangs (Rodgers, 1999). Again, this programme has not yet been evaluated, but may be worth exploring.

Other approaches are also likely to be needed alongside these, which are essentially approaches to the individual. For instance, an approach that may be effective in terms of reducing both substance misuse and violence is to reduce access to substances. One way to achieve this would be through improved policing, both so that the country's borders are sealed to organised crime groups, and so that existing alcohol laws are enforced – for instance, by closing unlicensed shebeens and insisting that licensed facilities obey legislated closing times (Parry, 2005). Working with shebeens in this way would need to be done with sensitivity, recognising that for many families the shebeen represents the sole source of income, and assisting them to develop other sources of income (for instance, by serving food as well as alcohol).

Ultimately, however, these programmes will have effects on individuals, but the greater problems of drugs, alcohol, violence and gangsterism will continue to recur until the broader conditions of society come to reflect a society in which the majority of its members are, as Amartya Sen might have it, free to fulfil their capabilities (Corbridge, 2002). This will require attention to our schools, so that they become resourced and capable of delivering quality education, and particularly to the work-school connection, so that there is a real purpose to going to school. In turn, this might mean attention largely to economic growth, and ensuring that schools are preparing learners with the skills demanded by that economic growth. When schools are functioning well, and there is widespread employment, then we might begin to see an end to what is essentially still a ghettoisation of so many South Africans (Wilson, 2003).

Conclusion

This chapter has attempted to show how South Africa's history of colonialism and apartheid has weakened families, schools and communities, and thereby created the conditions in

which the related problems of substance misuse and violence can flourish. These problems come together most notably in gangs, where substance use and violence are part of the intrinsic rituals of gangs, and provide gangs with the material goods that sustain them. Different ways of intervening in gangs are discussed, showing how substance abuse treatment should form a part of such interventions, and, similarly, how limiting access to substances may weaken gangs by removing their source of income. However, it is clear that both the existence of gangs and current high levels of substance misuse are related to the current structure of society. Improving our education system, strengthening families (for instance, by doing away with migrant labour) and increasing access to employment are critical factors in addressing both substance misuse and violence.

References

Bickford-Smith, V. (1990). The origins and early history of District Six to 1910. In S. Jeppie & C. Soudien (eds). *The Struggle for District Six: Past and Present*. Cape Town: Buchu Books; pp 35–42.

Bowley, D.M., Rein, P., Cherry, R., Vellema, J., Snyman, T. & Boffard, K.D. (2004). Substance abuse and major trauma in Johannesburg. *South African Journal of Surgery*, 42(1):7–10.

Bradshaw, D., Groenewald, P., Laubscher, P., Nannan, N., Nojilana, B., Norman, R., Pieterse, D., Schneider, M., Bourne, D.E., Timaeus, I.M., Dorrington, R. & Johnson, L. (2003). Initial burden of disease estimates for South Africa, 2000. *South African Medical Journal*, 93(9):682–88.

Bray, R., Gooskens, I., Kahn, L., Moses, S. & Seekings, J. (2010). *Growing Up in the New South Africa: Childhood and Adolescence in Post-apartheid Cape Town*. Cape Town: HSRC Press.

Catalano, R.F. & Hawkins, J.D. (1996). The social development model: a theory of antisocial behavior. In J.D. Hawkins (ed.). *Delinquency and Crime: Current Theories*. New York: Cambridge University Press; pp 198–235.

Christie, P. (1985). *The Right to Learn: The Struggle for Education in South Africa*. Johannesburg: Ravan Press.

Cooper, A. & Ward, C.L. (forthcoming). Intervening with youth in gangs. In C.L. Ward, A. van der Merwe & A. Dawes (eds), *Youth Violence in South Africa: Sources and Solutions*. Cape Town: HSRC Press.

Coovadia, H., Jewkes, R., Barron, P., Sanders, D. & McIntyre, D. (2009). The health and health system of South Africa: historical roots of current public health challenges. *Lancet*, 374(9692):817–34.

Corbridge, S. (2002). Development as freedom: the spaces of Amartya Sen. *Progress in Development Studies*, 2(3):183–217.

Dawes, A. & Ward, C.L. (2008). Levels, trends, and determinants of child maltreatment in the Western Cape Province. In R. Marindo, C. Groenewald & S. Gaisie (eds). *The State of the Western Cape Population.* Cape Town: HSRC Press; pp 97–125.

Dudley, R. (1990). Forced removals: the essential meanings of District Six. In S. Jeppie & C. Soudien (eds). *The Struggle for District Six: Past and Present*. Cape Town: Buchu Books; pp 197–203.

Ellickson, P., Saner, H. & McGuigan, K.A. (1997). Profiles of violent youth: substance use and other concurrent problems. *American Journal of Public Health*, 87(6):985–91.

Fiske, E. & Ladd, H. (2006). Racial equity in education: how far has South Africa come? *Perspectives in Education*, 24:95–108.

Gottfredson, M. & Hirschi, T. (1990). *A General Theory of Crime*. Stanford, CA: Stanford University Press.

Hart, D.M. (1990). Political manipulation of urban space: The razing of District Six, Cape Town. In S. Jeppie & C. Soudien (eds). *The Struggle for District Six: Past and Present*. Cape Town: Buchu Books; pp 117–42.

Horrell, M. (1970). *The Education of the Coloured Community in South Africa, 1652 to 1970*. Johannesburg: South African Institute of Race Relations.

Josi, D. & Sechrest, D. (1999). A pragmatic approach to parole aftercare: evaluation of a community reintegration program for high-risk youthful offenders. *Justice Quarterly*, 16(1):51–80.

Kalichman, S., Simbayi, L., Kaufman, M., Cain, D. & Jooste, S. (2007). Alcohol use and sexual risks for HIV/AIDS in sub-Saharan Africa: systematic review of empirical findings. *Prevention Science*, 8(2):141–51.

Kalichman, S., Simbayi, L., Vermaak, R., Jooste, S. & Cain, D. (2008). HIV/AIDS risks among men and women who drink at informal alcohol serving establishments (shebeens) in Cape Town, South Africa. *Prevention Science*, 9(1):55–62.

Le Blanc, M. (1997). A generic control theory of the criminal phenomenon: the structural and dynamic statements of an integrative multilayered control theory. In T.P. Thornberry (ed.). *Developmental Theories of Crime and Delinquency: Advances in Criminological Theory*. Vol. 7. New Brunswick, NJ: Transaction Publishers; pp 215–85.

Legget, T. (2005). Terugskiet (returning fire): growing up on the street corners of Manenberg, South Africa. In L. Dowdney (ed.). *Neither War nor Peace: International Comparisons of Children and Youth in Organised Armed Violence*. Rio de Janeiro: Viva Rio/ISER/IANSA; pp 296–315.

Lemon, A. & Battersby-Lennard, J. (2009). Overcoming the apartheid legacy in Cape Town schools. *Geographical Review*, 99(4):517–38.

Leoschut, L. & Burton, P. (2006). *How Rich the Rewards? Results of the 2005 National Youth Victimisation Study*. Cape Town: Centre for Justice and Crime Prevention.

Limber, S.P. (2006). The Olweus Bully Prevention Program: an overview of its implementation and research basis. In S.R. Jimerson & M. Furlong (eds). *Handbook of School Violence and School Safety: From Research to Practice*. Mahwah, NJ: Lawrence Erlbaum Associates; pp 293–307.

London, L. (1999). The 'dop' system, alcohol abuse and social control amongst farm workers in South Africa: a public health challenge. *Social Science and Medicine*, 48(2): 1407–14.

Louw, A. (1997). Surviving the transition: trends and perceptions of crime in South Africa. *Social Indicators Research*, 41(1/3):137–68.

Mager, A. (2004). 'White liquor hits black livers': meanings of excessive liquor consumption in South Africa in the second half of the twentieth century. *Social Science and Medicine*, 59(4):735–51.

Mager, A.K. (2008). Apartheid and business: Competition, monopoly and the growth of the malted beer industry in South Africa. *Business History*, 50(3):272–90.

May, P.A., Brooke, L., Gossage, J.P., Croxford, J., Adnams, C., Jones, K.L., Robinson, L. & Viljoen, D. (2000). Epidemiology of fetal alcohol syndrome in a South African community in the Western Cape Province. *American Journal of Public Health*, 90(12):1905–12.

Mokwena, S. (1991). The era of the Jackrollers: contextualising the rise of the youth gangs in Soweto. Johannesburg: Centre for the Study of Violence and Reconciliation. Available from: http://www.csvr.org.za/wits/papers/papmokw.htm; accessed 3 August 2011.

Morojele, N., Kachieng'a, M., Mokoko, E., Nkoko, M., Parry, C.D.H., Nkowane, A., Moshia, K. & Sazena, S. (2006). Alcohol use and sexual behaviour among risky drinkers and bar and shebeen patrons in Gauteng province, South Africa. *Social Science and Medicine*, 62(1)217–27.

Myers, B., Louw, J. & Fakier, N. (2008). Alcohol and drug abuse: removing structural barriers to treatment for historically disadvantaged communities in Cape Town. *International Journal of Social Welfare*, 17(2):156–65.

Nasson, B. (1990). Oral history and the reconstruction of District Six. In S. Jeppie & C. Soudien (eds). *The Struggle for District Six: Past and Present*. Cape Town: Buchu Books; pp 44–66.

Nleya, N. (2008). Development policy and water services in South Africa: an urban poverty perspective. *Development Southern Africa*, 25(3):269–81.

Norman, R., Matzopoulos, R., Groenewald, P. & Bradshaw, D. (2007). The high burden of injuries in South Africa. *Bulletin of the World Health Organization*, 85(9):695–702.

Olds, D., Hill, P. & Rumsey, E. (1998). Prenatal and early childhood nurse home visitation. *Juvenile Justice Bulletin*, November 1998. Rockville, MD: US Department of Justice. Available from: http://www.ncjrs.gov/html/ojjdp/172875/contents.html; accessed 3 July 2009.

Parry, C.D.H. (2005). A review of policy-relevant strategies and interventions to address the burden of alcohol on individuals and society in South Africa. *South African Psychiatry Review*, 8(1):20–24.

Parry, C.D.H., Plüddemann, A., Donson, H., Sukhai, A., Marais, S. & Lombard, C. (2005). Cannabis and other drug use among trauma patients in three South African cities, 1999-2001. *South African Medical Journal*, 95(6):429–32.

Parry, C.D.H., Plüddemann, A., Steyn, K., Bradshaw, D., Norman, R. & Laubscher, R. (2005). Alcohol use in South Africa: findings from the first Demographic and Health Survey (1998). *Journal of Studies on Alcohol*, 66(1):91–97.

Parry, C.D.H., Tibbs, J., Van der Spuy, J. & Cummins, G. (1996). Alcohol attributable fractions for trauma in South Africa. *Curiationis*, 19(1):2–5.

Peden, M., Van der Spuy, J., Smith, P. & Bautz, P. (2000). Substance abuse and trauma in Cape Town. *South African Medical Journal*, 90(3):251–55.

Pinnock, D. (1982). Towards an Understanding of the Structure, Function and Cause of Gang Formation in Cape Town. Cape Town: Institute of Criminology, University of Cape Town.

Pinnock, D. (1984). *The Brotherhoods: Street Gangs and State Control in Cape Town*. Cape Town: David Philip.

Plüddemann, A., Dada, S., Parry, C., Bhana, A., Perreira, T., Carelsen, A., Kitleli, N., Gerber, W., Rosslee, C. & Fourie, D. (2009). *SACENDU Research Brief Vol. 12(1): Monitoring alcohol and drug abuse trends in South Africa (July 1996–December 2008)*. Cape Town: Medical Research Council.

Plüddemann, A., Flisher, A.J., Mathews, C., Carney, T. & Lombard, C. (2008). Adolescent methamphetamine use and sexual risk behaviour in secondary school students in Cape Town, South Africa. *Drug and Alcohol Review*, 27(6):687–92.

Plüddemann, A., Parry, C., Donson, H. & Sukhai, A. (2004). Alcohol use and trauma in Cape Town, Durban and Port Elizabeth, South Africa: 1999–2001. *Injury Control and Safety Promotion*, 11(4):265–67.

Presidency, Republic of South Africa. (2009). *Development Indicators 2009*. Available from: www.info.gov.za/view/DownloadFileAction?id=109313; accessed 3 August 2011.

Richter, L.M. & Dawes, A.R.L. (2008). Child abuse in South Africa: rights and wrongs. *Child Abuse Review*, 17(2):79–93.

Rodgers, D. (1999). *Youth Gangs and Violence in Latin America and the Caribbean: A Literature Survey*. LCR Sustainable Development Working Paper No. 4. Washington, DC: The World Bank.

Schram, P. & Gaines, L. (2005). Examining delinquent nongang members and delinquent gang members: a comparison of juvenile probationers at intake and outcomes. *Youth Violence and Juvenile Justice*, 3(2):99–115.

Spergel, I. (1995). *The Youth Gang Problem: A Community Approach*. New York: Oxford University Press.

Standing, A. (2005). *The Threats of Gangs and Anti-gangs Policy: Policy Discussion Paper.* Pretoria: Institute for Security Studies.

Steinberg, J. (2004). *The Number: One Man's Search for Identity in the Cape Underworld and Prison Gangs*. Jeppestown: Jonathan Ball Publishers.

Townsend, L., Flisher, A.J. & King, G. (2007). A systematic review of the relationship between high school dropout and substance use. *Clinical Child and Family Psychology Review*, 10(4):295–317.

Tremblay, R., Mâsse, L., Pagani, L. & Vitaro, F. (1996). From childhood physical aggression to adolescent maladjustment: the Montreal Prevention Experiment. In R. Peters & R. McMahon (eds). *Preventing Childhood Disorders, Substance Abuse and Delinquency*. Thousand Oaks, CA: Sage Publications; pp 268–98.

USAID (2006). *Central America and Mexico Gang Assessment*. Report prepared for USAID Bureau for Latin American and Caribbean Affairs Office of Regional Sustainable Development. Available from http://www.usaid.gov/gt/docs/gangs_assessment.pdf; accessed 3 July 2009.

Ward, C.L. & Bakhuis, K. (2009). Indigenous theories of children's involvement in gangs: Cape Town's young people speak out. *Children & Society*, 24:50–62.

Ward, C.L., Mertens, J.R., Flisher, A.J., Bresick, G.F., Sterling, S.A., Distiller, G.B. & Weisner, C.M. (2005). Substance abuse and HIV risk behaviours in Cape Town primary health care service users. *South African Psychiatry Review*, 8(4):160–65.

Ward, C.L., Mertens, J.R., Flisher, A.J., Bresick, G.F., Sterling, S.A., Little, F. & Weisner, C.M. (2008). Prevalence and correlates of substance use among South African primary care clinic patients. *Substance Use and Misuse*, 43(10):1395–1410.

Wegner, L., Flisher, A.J., Chikobvu, Pl, Lombard, C. & King, G. (2008). Leisure boredom and high school dropout in Cape Town, South Africa. *Journal of Adolescence*, 31(3):421–31.

Western, J. (1981). *Outcast Cape Town*. Minneapolis: University of Minnesota Press.

Wilson, W.J. (2003). Race, class and urban poverty: a rejoinder. *Ethnic and Racial Studies*, 26(6):1096–114.

Yamauchi, F. (2005). Race, equity, and public schools in post-apartheid South Africa: equal opportunity for all kids. *Economics of Education Review*, 24(2):213–33.

16 Substance use, stigma and health literacy: a conceptual framework

Katherine R. Sorsdahl and Dan J. Stein

Introduction

Substance use represents a major public health problem, both globally and in South Africa. Results from the South African Stress and Health Study (SASH), the first nationally representative study of psychiatric morbidity in South Africa, indicate a high lifetime prevalence (13.3%) and early onset (21 years) of substance use (Stein et al, 2008). Despite this high prevalence of substance use, SASH revealed that only 27.6% of South Africans who met the criteria for substance use disorder (see Chapter 2 for definitions) received treatment in the year preceding the interview (Seedat et al, 2008). The consequences of untreated psychiatric disorders for the individual and society are staggering. For example, alcohol use was responsible for 7.1% of all deaths and 7.0% of all the disability-adjusted life-years lost in South Africa in 2000 (Schneider et al, 2007).

Yet, there is substantial evidence to suggest that drug and psychotherapeutic interventions are effective in the treatment of individuals suffering from substance use disorders (Miller, 2009). Providing treatment at an early stage has the potential to prevent enormous disability before the illness becomes more severe and more difficult to treat. However, a number of barriers to receiving adequate mental health care are described in the literature, such as poor access to or lack of available services (Emsley, 2001; Flisher et al, 1997; Kohn et al, 2004).

Potential reasons for not seeking treatment for substance use include stigmatisation and low mental health literacy. In SASH, the most frequently cited reason for not seeking professional treatment for mental disorders was a low perceived need for treatment (93%), followed by psychological barriers (7.4%), with stigma much less commonly cited (0.6%) (Brewer et al, 2011). However, a cross-national study conducted by the World Health Organization (WHO) in 14 countries examined 18 of the most stigmatised conditions (eg, being a criminal, HIV-positive or homeless) and found that alcohol addiction was ranked as the fourth most stigmatised, while other drug addiction was ranked as the most stigmatised (Room et al, 2001).

The stigmatisation process

Over the years, a number of theorists have developed conceptual frameworks for understanding the structural and social processes that contribute to stigma (Goffman, 1963; Link & Phelan, 2001; Jones et al, 1984; Elliot et al, 1982). There is ongoing debate regarding the definition and the utility of the concept of stigma, and none of these conceptualisations

should be viewed as definitive (Link et al, 2004). The most frequently cited conceptual model of stigma is that of Goffman, who used the term 'stigma' to 'refer to an attribute that is deeply discrediting' (Goffman, 1963:3). Inherent in this definition is the idea that this attribute is something which deviates from what society believes to be 'normal' and can be a physical marking or a behaviour (Goffman, 1963).

The influence of Goffman's work is evident in the work of more recent researchers who draw on his work frequently when seeking definitions of stigma. In a review of population-based attitude research in psychiatry during the past 15 years, however, only two theoretical models were found to have been empirically tested using a population-based method (Angermeyer & Dietrich, 2006). These include a social psychological perspective on public stigma by Corrigan and Watson (2002) and a sociological concept of the stigma process by Link & Phelan (2001).

According to Corrigan & Watson (2002), stigma can be categorised as either public stigma or self-stigma. Public stigma refers to the reaction of the general public to a certain group of individuals based on the stigma that is attached to this group. It comprises three components: stereotype, prejudice and discrimination. Stereotypes are collectively shared beliefs about a group of individuals, which are generally familiar to everyone, but not necessarily adopted. If they are adopted, prejudices develop, resulting in negative emotional reactions and ultimately discriminatory behaviour.

According to Link and Phelan (2001) there are five components of stigma: labelling, stereotyping, separation, status loss and discrimination within the context of power differentials. *Labelling* occurs when people distinguish and label human differences. *Stereotyping* is when labelled differences are linked to stereotypes which are deemed by others to be undesirable. *Separation* occurs when labelled people are placed in distinct categories so as to accomplish some degree of separation between 'us' and 'them'. *Status loss and discrimination* occur when stigma interferes with an individual's ability to participate fully in the social and economic life of her/his community. When individuals lose status or are discriminated against because of their negatively evaluated differences, they experience enacted stigma.

In the developed world, a number of attempts have been made to measure the stigma associated with mental illness in general. Most of these have focused on attitudes towards mental illness held by people in the community (Link et al, 2004). Far fewer attempts have been made to measure stigma directly with service users themselves. However, in recent years, many authors argue that at least three conceptually distinct forms of stigma can be identified: enacted/experienced stigma, anticipated/perceived stigma and internalised/self-stigma (Brohan et al, 2010; Luoma et al, 2007; Link & Phelan, 2001). *Enacted* stigma refers to the extent to which people with a mental illness are actually discriminated against by others because they have, or are thought to have, a mental disorder. *Anticipated* stigma refers to the degree to which individuals with a mental illness anticipate they will experience prejudice and discrimination, and *internalised* stigma refers to the degree to which individuals with a mental illness endorse the negative beliefs and feelings associated with having a mental disorder. Of the 57 studies that were included in a narrative literature review of stigma, 7 addressed aspects of perceived stigma, 10 aspects of enacted stigma and 5 aspects of internalised stigma (Brohan et al, 2010).

Relatively little empirical work to date has focused on substance use disorders (see below). Recently, however, a self-report measure of perceived stigma for substance users has been developed and studied (Luoma et al, 2010). This kind of work provides a useful foundation for moving forward. It can be hypothesised that substance users face stigma in its various forms, including enacted, perceived and self-stigma.

Stigma and substance use

Stigma may vary markedly across different mental disorders. In a review of population-based attitude research in psychiatry, individuals with a psychiatric disorder were viewed as being in need of help, dependent on others and unpredictable (Angermeyer & Dietrich, 2006). The attribute of unpredictability was more commonly reported for people with schizophrenia (54–85%) or alcoholism (71%) than for people with depression (28–56%) or anxiety disorders (50%). People with mental disorders were less often considered violent and dangerous, but such considerations were more commonly present in people with schizophrenia (18–71%) and alcoholism (65–71%). Two studies investigating the stigma associated with psychiatric disorders in a community and an HIV-positive sample in South Africa found similar results, with alcoholism highly stigmatised compared to other psychiatric disorders (Sorsdahl & Stein, 2010; Sorsdahl et al, 2010). Healthcare workers have also been found to view substance users as irresponsible and more aggressive, dangerous and untrustworthy (Hopwood, Treloar & Bryant, 2006; Kelly & Westerhoff, 2010).

Substance-related conditions may be particularly susceptible to stigma via attributions of personal culpability associated with attribution theory (see Gilbert & Malone, 1995; Ross, 1977). The general community may view substance users as having the ability to take control of their behaviour if they really wanted, since alcohol and other drug use initially involves an individual's free choice to experiment. This belief is not, however, consistent with research demonstrating that substance use disorders are associated with significant structural and functional abnormalities which underlie failures to control behaviour despite its harmful consequences (Edwards & Gross, 1976; Koob & Le Moal, 2006).

Relatively few studies have evaluated stigma experiences directly in individuals with a mental illness. However research indicates that experiences of stigma, whether enacted, perceived or self-stigma, can have serious consequences for individuals. Enacted stigma has been associated with multiple negative outcomes such as unemployment (eg, Link, 1987), housing problems (eg, Penn & Martin, 1998) and difficulty in social adjustment (eg, Perlick et al, 2001). Internalised stigma is associated with delays in treatment-seeking (eg, Starr, Campbell & Herrick, 2002), diminished self-esteem/self-efficacy (eg, Corrigan & Watson, 2002) and lower quality of life (eg, Rosenfield, 1997). Perceived stigma is associated with less positive views of treatment (Givens et al, 2007) and decreased stated willingness to seek mental health treatment (Barney et al, 2006; Sirey et al, 2001).

Some of this research has focused on stigma in subjects with substance use disorders. Substance-abusing individuals have reported fear of stigma as a reason for not seeking treatment (Cunningham et al, 1993; Sobell, Sobell & Toneatto, 1992). Ahern, Stuber and Galea (2007) investigated the associations of stigma and discrimination with physical and mental health and found that alienation (ie, internalisation of the belief that drug users

are marginal members of society) and experiences of discrimination were independently associated with poorer mental health, while discrimination was associated with poorer physical health. Perceived devaluation (ie, the belief that most people endorse common negative stereotypes about drug users) was not significantly associated with poorer mental or physical health. Luoma et al (2007) examined the role of stigma towards substance abuse in people in recovery from substance use problems and found high levels of enacted, perceived and internalised stigma. Particularly striking was the finding that internalised stigma was more highly related to measures of psychological functioning and quality of life than enacted and perceived stigma (Luoma et al, 2007).

Overall, the available literature indicates that, compared to other psychiatric disorders, substance use seems to be considered outside the realm of medical disorders and within the realm of individual choice and responsibility, increasing the likelihood of stigmatisation. Although people with a mental illness are generally more likely to be seen as more responsible for causing their illness than are people with a physical illness, this is particularly true for those with substance use disorders.

Mental health literacy and substance use

The term 'mental health literacy' was first coined by Anthony Jorm and colleagues, and is defined as the 'knowledge and beliefs about mental illness that aid their recognition, management or prevention' (Jorm et al, 1997). Mental health literacy has the potential to influence help-seeking behaviour and holds serious implications for adherence to treatment (Jorm et al, 1997; Wright et al, 2007). Although a number of studies have been conducted assessing mental health literacy (Angermeyer & Dietrich, 2006), these focus almost exclusively on depression and schizophrenia (Angermeyer & Matschinger, 1996; Jorm, Christensen & Griffiths, 2006; Jorm et al, 2006; Lauber et al, 2001) rather than on substance use disorders.

However, a few studies have investigated mental health literacy using vignettes, and have included vignettes on substance use (Link et al, 1999; Sorsdahl & Stein, 2010; Sorsdahl et al, 2010). Three of these four studies were conducted in South Africa, and compared the mental health literacy of a number of mental disorders, including alcohol use (see above). Link et al (1999) used a vignette of alcohol dependence, cocaine dependence schizophrenia, major depression or a troubled person to elicit community beliefs and knowledge about mental disorders. Results indicated that the alcohol and cocaine dependence vignettes were the least likely to be considered a mental disorder. The most commonly endorsed cause for alcohol dependence was the way the person was raised, and for cocaine dependence it was the person's own bad character. The person depicted with a cocaine dependence problem was perceived as the most likely to be violent, followed in order by those depicted in the vignettes for alcohol dependence, schizophrenia, major depression and troubled person.

There is some evidence to suggest that population-wide and individual level interventions designed to improve mental health literacy are effective (Jorm, Christensen & Griffiths, 2006). Unfortunately, none to date have focused on substance use. Beyond Blue is a programme aimed to increase the awareness of depression in a number of states in Australia. In order to assess the programme's impact, data from the 1995 and 2004 Australian national surveys,

which included a measure of mental health literacy, were compared to assess whether states and territories that funded the programme (high-exposure states) differ from those that did not (low-exposure states). There was a significant change in beliefs and treatments in the high-exposure states, although recognition of depression in the vignettes also improved substantially at a national level. Additionally, a review of three studies (two RCTs) evaluating mental health first-aid training in Australia resulted in promising findings. There were statistically significant differences five to six months following the training in recognition of disorders in vignettes and beliefs about treatments, including medications (Kitchener & Jorm, 2006). Nevertheless, it has not yet been shown that improved mental health literacy leads to improved mental health (Jorm et al, 2006).

Theoretical framework

Stein (2008) has proposed that there are different approaches to thinking through the concept of disease. To some extent, the different views proposed can be divided into three. However, this is a heuristic classification and not intended to encompass the views of all authors.

First, there is a 'classical' view. The classical view has a long history. It can be traced to early philosophical concepts of science and of medicine, and has commonalities with the views of positivist philosophy. A classical approach attempts to define the necessary and sufficient criteria of a range of constructs, including disorders. For example, a square is defined as having four features: 1) four sides; 2) four angles; 3) all sides equal; and 4) all angles equal.

Second, there is a 'critical' view. This too has a long history. There is a substantial tradition of criticising the classical approach to science and medicine, arguing that its constructs merely reflect one particular way of looking at the world, which is not necessarily privileged. This view argues that disease is a relativistic construct, changing from place to place, and time to time, rather than a universal form.

Third, the 'integrative' approach argues that although science is a social process, and although medical diagnosis reflects particular values, knowledge of the mechanisms responsible for disease is possible, and advances in such knowledge allow us to improve our diagnostic schemas. An integrative approach seems consistent with a range of empirical work that has explored the way in which scientific and medical constructs operate.

Consider, for example, work on typical and atypical constructs. When presented with a list of different birds (robin, owl, ostrich), research subjects agree on which kinds of birds are typical (eg, robin), which are less typical (eg, owl) and which are atypical (eg, ostrich) (Rosch, 1978). Similarly, it seems that we view certain diseases as typical, while others are seen as atypical.

A typical disease, such as a bacterial infection, appears to be associated with various characteristics. In particular, there is clear distress and/or impairment, the patient is not responsible for getting ill, medical interventions are administered, and during this time the person adopts the 'sick role'. In an atypical disease, such as a condition requiring cosmetic surgery, there may be more debate about the extent of associated distress and/or impairment, about the responsibility of the patient to accept their condition, about whether the intervention is a treatment or an enhancement, and about whether the person deserves the sick role.

We would argue that substance use is more an atypical disease. From a medical perspective, there is certainly strong evidence that substance use disorders are associated with considerable distress and/or impairment, that they are associated with particular genes, that they respond to medical interventions, and that a 'sick role' is appropriate. At the same time, and from the perspective of many clinicians and laypersons, it is true that those with substance use bear significant responsibility for starting to use substances, and also bear significant responsibility for reversing their pattern of substance use.

Given that substance use disorders are atypical, we would argue that an approach that focuses simply on trying to decrease stigma may not be successful. Such an approach may not put sufficient emphasis on the responsibility of substance users, to be persuasive to clinicians or other stakeholders. Instead, we would emphasise the importance of an approach that focuses on increasing mental health literacy. Such an approach would allow an emphasis on the many factors that predispose individuals to substance use disorders, on the psychobiological mechanisms that underlie substance use disorders and that contribute to individuals' inability to simply stop using substances, and on the available treatments for substance use disorders, many of which encourage substance users to take responsibility for the management of their illness.

Much of the work on stigma seems to rely either on a classical perspective of disorder (in which disease is simply an objective construct and does not entail social values), or a critical perspective (in which there is a strong emphasis on the importance of labelling and there is no objective basis for making judgments about behaviours such as substance use). From an integrative perspective, substance use disorders are complex phenomena. Those who suffer from them deserve treatment, but they also have a responsibility to fight against their own impulses to use substances. Indeed, since Plato, philosophers have argued that crimes committed while under the influence of drugs are deserving of punishment. This argument relies on knowledge of the complexities of substance use disorders. It is incumbent on clinicians and researchers in the substance use field to advance our knowledge of these disorders, to ensure dissemination of knowledge about substance use disorders, and to contribute to increased substance use literacy.

Conclusion

We began this chapter by noting that despite the high prevalence of substance use disorders, there is significant underdiagnosis and undertreatment. We noted that substance use disorders are more stigmatised than other mental disorders, a finding which raises the possibility that reducing such stigma will remove treatment barriers. We also briefly summarised work on mental health literacy, noting that attempts to increase mental health literacy may contribute to more accurate views of mental disorders, and to increased treatment seeking. Finally, we raised the question of whether substance use disorders were best viewed as 'atypical' medical disorders. This would explain why clinicians and laypersons so often view substance users as responsible for their behaviours, and would encourage interventions that increase substance use literacy so that there would be greater understanding of how this position is both correct (substance users are legitimately required to assume responsibility for aspects of their illness and its treatment) and incorrect (the way

in which substances alter the brain and diminish impulse control must be acknowledged). Further empirical research is needed in order to delineate fully the arguments here, and to establish whether they are of benefit to those with substance use disorders.

References

Ahern, J., Stuber, J. & Galea, S. (2007). Stigma, discrimination and the health of illicit drug users. *Drug and Alcohol Dependence*, 88(2–3):188–96.

Brewer, B., Sorsdahl, K., Harrison, J., Stein, D., Seedat, S. & Williams D. (2011). Barriers to mental health treatment care and predictors of treatment dropout in the South African Stress and Health Study. *Psychiatric Services*, 62(7):774–81

Angermeyer, M.C. & Dietrich, S. (2006). Public beliefs about and attitudes towards people with mental illness: a review of population studies. *Acta Psychiatrica Scandinavica*, 113(3):163–79.

Angermeyer, M. & Matschinger, H. (1996). Public attitude towards psychiatric treatment. *Acta Psychiatrica Scandinavica*, 94(5):326–36.

Barney, L.J., Griffiths, K.M., Jorm, A.F. & Christensen, H. (2006). Stigma about depression and its impact on help-seeking intentions. *The Australian and New Zealand Journal of Psychiatry*, 40(1):51–54.

Brohan, E., Slade, M., Clement, S. & Thornicroft, G. (2010). Experiences of mental illness stigma, prejudice and discrimination: a review of measures. *BMC Health Services Research*, 10:80.

Corrigan, P.W. & Watson, A.C. (2002). Understanding the impact of stigma on people with mental illness. *World Psychiatry*, 1(1):16–20.

Cunningham, J.A., Sobell, L.C., Sobell, M.B., Agrawal, S. & Toneatto, T. (1993). Barriers to treatment: Why alcohol and drug abusers delay or never seek treatment. *Addictive Behaviors*, 18(3):347–53.

Edwards, G. & Gross, M.M. (1976). Alcohol dependence: provisional description of a clinical syndrome. *British Medical Journal*, 1(6017):1058–61.

Elliot, G.C., Ziegler, H.L., Altman, B.M. & Scott, D. R. (1982). Understanding stigma: dimensions of deviance and coping. *Deviant Behaviour*, 3(3):275–300.

Emsley, R. (2001). Focus on psychiatry in South Africa. *British Journal of Psychiatry*, 178:382–86.

Flisher, A., Ricctelli, G., Jhetam, N. & Robertson, B. (1997). A survey of professional activities of psychiatrists in South Africa. *Psychiatric Services*, 48(5):707–709.

Gilbert, D.T. & Malone, P.S. (1995). The correspondence bias. *Psychological Bulletin*, 117(1):21–38.

Givens, J.L., Katz, I.R., Bellamy, S. & Holmes, W. C. (2007). Stigma and the acceptability of depression treatments among African Americans and Whites. *Journal of General Internal Medicine*, 22(9):1292–97.

Goffman, E. (1963). *Stigma: Notes on the Management of Spoiled Identity.* Englewood Cliffs, NJ: Prentice Hall.

Hopwood, M., Treloar, C. & Bryant, J. (2006). Hepatitis C and injecting-related discrimination in New South Wales, Australia. *Drugs: Education, Prevention and Policy*, 13(1):61–75.

Jones, E., Farina, A., Hastorf, F., Markus, H., Miller, D. & Scott, R. (1984). *Social Stigma: The Psychology of Marked Relationships*. New York: W.H. Freeman & Co.

Jorm, A., Barney, L., Christensen, H., Highet, N., Kelly, C. & Kitchener, B. (2006) Research on mental health literacy: what we still need to know. *Australian and New Zealand Journal of Psychiatry*, 40(1):3–5.

Jorm. A., Christensen, H. & Griffiths, K. (2006). Changes in depression awareness and attitudes in Australia: the impact of beyondblue: the national depression initiative. *Australian and New Zealand Journal of Psychiatry*, 40(1):42–46.

Jorm, A., Korten, A., Jacomb, P., Christensen, H., Rodgers, B. & Pollitt, P. (1997). 'Mental health literacy': a survey of the public's ability to recognise mental disorders and their beliefs about the effectiveness of treatment. *Medical Journal of Australia*, 166(4): 182–86.

Kelly, J. & Westerhoff, C.M. (2010). Does it matter how we refer to individuals with substance-related conditions? A randomized study of two commonly used terms. *International Journal of Drug Policy*, 21(3):202–207.

Kitchener, B. & Jorm, A. (2006). Mental health first aid training: review of evaluation studies. *Australian and New Zealand Journal of Psychiatry*, 40(1):6–8.

Kohn, R., Szabo, C., Gordon, A., & Allwood, C. (2004). Race and psychiatric services in post-apartheid South Africa: A preliminary study of psychiatrists perceptions. *International Journal of Social Psychiatry*, 50(1):18–24.

Koob, G.F. & Le Moal, M. (2006). *Neurobiology of Addiction*. London: Academic Press.

Lauber, C., Nordt, C., Falcato, L. & Rössler, W. (2001). Lay recommendations on how to treat mental disorders. *Social Psychiatry Psychiatric Epidemiology*, 36(11):553–56.

Link, B.G. (1987). Understanding labeling effects in the area of mental disorders: an assessment of the effect of expectations of rejection. *American Journal of Community Psychology*, 11:261–73.

Link, B.G., Phelan, J.C., Bresnahan, M. & Pescolsolido, B.A. (1999). Public conceptions of mental illness: labels, causes, dangerousness, and social distance. *American Journal of Public Health*, 89(9):1328–33.

Link, B.G. & Phelan, J.C. (2001). Conceptualizing stigma. *Annual Review of Sociology*, 27:363–85.

Link, B.G., Yang, L.H., Phelan, J.C., & Collins, P.Y. (2004). Measuring mental illness stigma. *Schizophrenia Bulletin*, 30(3):511–41.

Luoma, J.B., O'Hair, A.K., Kohlenberg, B.S., Hayes, S.C. & Fletcher, L. (2010). The development and psychometric properties of a new measure of perceived stigma toward substance users. *Substance Use & Misuse*, 45(1–2):47–57.

Luoma, J.B., Twohig, M.P., Waltz, T., Hayes, S.C., Roget, N., Padilla, M. & Fisher, G. (2007). An investigation of stigma in individuals receiving treatment for substance abuse. *Addiction Behaviors*, 32(7):1331–46.

Miller P. (2009). *Evidence-based Addiction Treatment*. New York: Academic Press.

Penn, D.L. & Martin, J. (1998). The stigma of severe mental illness: some potential solutions for a recalcitrant problem. *Psychiatric Quarterly*, 69(3):235–47.

Perlick, D.A., Rosenheck, R.A., Clarkin, J.F., Sirey, J.A., Salahi, J., Struening, E.L. & Link, B.G. (2001). Adverse effects of perceived stigma on social adaptation of persons diagnosed with bipolar affective disorder. *Psychiatric Services*, 52(12):1627–32.

Room, R., Rehm, J., Trotter, R.T., Paglia, A. &. Üstün, T.B. (2001). Cross-cultural views on stigma valuation parity and societal attitudes towards disability. In T.B. Üstün, S. Chatterji, J.E. Bickenbach, R.T. Trotter II, R. Room & J. Rehm et al (eds). *Disability and Culture: Universalism and Diversity*. Seattle: Hofgrebe & Huber; pp 247–91.

Rosch, E. (1978). Principles of categorization. In E. Rosch & B.B. Lloyd. *Cognition and Categorization*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Rosenfield, S. (1997). Labelling mental illness: the effects of received services and perceived stigma on life satisfaction. *American Sociological Review*, 62(4):660–72.

Ross, L. (1977). The intuitive psychologist and his shortcomings: distortions in the attribution process. In L. Berkowitz (ed.). *Advances in Experimental Psychology*. New York: Academic Press; pp 173–220.

Schneider, M., Norman, R., Parry, C., Bradshaw, D. & Plüddemann, A. (2007). Estimating the burden of disease attributable to alcohol use in South Africa in 2000. *South African Medical Journal*, 97(8):664–72.

Seedat, S., Stein, D. J., Herman, A., Kessler, R., Sonnega, J., Heeringa, S. Williams, S. & Williams, D. (2008). Twelve-month treatment of psychiatric disorders in the South African Stress and Health Study (World Mental Health Survey Initiative). *Social Psychiatry and Psychiatric Epidemiology*, 43(11):889–97.

Sirey, J.A., Bruce, M.L., Alexopoulos, G.S., Perlick, D.A., Raue, P., Friedman, S.J. & Meyers, B.S. (2001). Perceived stigma as a predictor of treatment discontinuation in young and older outpatients with depression. *The American Journal of Psychiatry*, 158(3):479–81.

Sobell, L.C., Sobell, M.B. & Toneatto, T. (1992). Recovery from alcohol problems without treatment. In N. Heather, W.R. Miller & J. Greeley (eds). *Self-control and the Addictive Behaviors*. New York: Maxwell Macmillan; pp 198–242.

Sorsdahl, K., Mall, S., Stein, D. & Joska, J. (2010). Perspectives towards mental illness in people living with HIV/AIDS in the Western Cape of South Africa. *Aids Care*, 22(11):1418–27.

Sorsdahl, K. & Stein, D. (2010). Knowledge of and stigma associated with mental disorders in a South African community sample. *Journal of Nervous and Mental Disease*, 198(10):742–47.

Starr, S., Campbell, L.R. & Herrick, C.A (2002). Factors affecting use of the mental health system by rural children. *Issues in Mental Health Nursing*, 23(3):291–304.

Stein, D.J. (2008). *Philosophy of Psychopharmacology: Smart Pills, Happy Pills, and Pep Pills*. Cambridge: Cambridge University Press.

Stein, D.J., Seedat, S., Herman, A., Moomal, H., Heeringa, S.G., Kessler, R.C. & Williams, D.R. (2008). Lifetime prevalence of psychiatric disorders in South Africa. *British Journal of Psychiatry*, 192(2):112–17.

Wright, A., Jorm, A., Harris, M. & McGorry, P. (2007). What's in a name? Is accurate recognition and labelling of mental disorders by young people associated with better help-seeking and treatment preferences? *Social Psychiatry and Psychiatric Epidemiology*, 42(3):244–50.

17 Addiction: philosophy and ethics

Willem Pienaar

Introduction

One of the main aims of philosophy is to ask fundamental ethical questions regarding life and relationships. Ethics is the generic term used for examining and making sense of moral life, while bioethics investigates moral issues in the field of medicine. We as medical practitioners often face difficult moral questions, the answers to which are frequently elusive. Since medical science is still 'imperfect', no healthcare worker can escape making judgment calls.

Previous chapters have raised the question of whether addiction is an illness (chapters 11 & 16), of the close relationship between social context and risk for addiction (Chapter 15). In this chapter, we will deal with the illness concept of addiction and the ethical dilemmas faced by healthcare workers when the illness may render the addict 'incapable' of making decisions in his or her own best interests. The focus of this discussion concerns the ethics of treating addiction to habit-forming drugs. The broader spectrum of 'addiction', eg, pathological gambling, sex addiction or addiction to any entity other than substances, will not be included in this chapter.

The burden of addiction in today's society

Why is drug abuse so widespread, occurring in most societies and communities throughout the world? Aldous Huxley (1951) seemed to understand people's desire to retreat from the harsh realities of life when he wrote:

> That humanity at large will ever be able to dispense with Artificial Paradises seems very unlikely. Most men and women lead lives at the worst so painful, at best so monotonous, poor and limited, that the urge to escape, the longing to transcend themselves if only for a few moments, is and always has been one of the principal appetites of the soul. (Huxley, 1951)

Drug abuse is here to stay – along with all the harmful social and personal consequences associated with it. Most therapists working in the field of drug abuse and addiction would agree that drugs will always be in supply as long as there is a demand for them. No amount of legislation, not even rigorously enforced regulation of the drug trade, will be capable of diminishing drug consumption. If the regulation of illicit drugs were to be made less stringent, drug consumption would rise. Strict regulation, on the other hand (such as that pertaining to opiates), results in illegal consumption, with dire consequences to society, including those deriving from activities carried out by drug lords and drug cartels (Marks, 1996).

The concept of addiction as an illness

Before we try to answer philosophical questions on the appropriate responses of clinicians and/or the community in managing this ubiquitous phenomenon, it must be emphasised that contemporary scientific knowledge underpinning addiction should at all times guide clinical decisions and action.

Since it is clear that this age-old, highly prevalent problem is real, bringing with it a huge burden both for the user and for the community, we need to address the following salient questions: does this phenomenon fulfil the definition of an illness? Such a label would imply that appropriate management should fall within the field of medicine. And, if it were to be considered an illness, can this phenomenon be prevented or controlled? Can it be managed or treated?

What is the definition of an illness? A patient is suffering from an illness if: he or she presents with a recognised cluster of symptoms; the clinician can elicit a known cluster of psychological (psychiatric) or physical signs; there is associated distress and/or impairment; special investigations confirm the presence of a specific illness; the illness has a known cause or specific aetiology; after appropriate treatment the patient would most likely show an expected response and final outcome.

An illness causes harm and suffering to the person. Although contemporary science has by no means reached the final answers to diagnostic criteria, classification systems, causes, final treatment modalities and known outcomes of all human illnesses, substance dependence fulfils the above definition of an illness in that there is a large body of evidence giving credence to the neurobiological underpinnings and causes of addiction. Furthermore, specific symptoms and signs associated with the various addictions have been clearly formulated and specific treatments are available and are largely efficacious. It can thus be said that addiction is a neuropsychiatric illness which falls within the responsibility of the health sciences.

Why do some people become addicted to substances?

Current knowledge on the causes, clinical course and treatment outcomes of addiction is complex and certainly incomplete. Science would have it that some individuals are genetically predisposed to the development of addiction, rendering some individuals protected and some vulnerable towards drug use and eventual addiction. Repeated exposure to drugs produces neuro-adaptation, particularly involving the brain's reward pathways, inducing a 'motivation' to continue using the drug. These biological changes of the reward system may be permanent, or at least long-lasting. The psychological effects of intoxication are personally experienced (ie, show marked inter-individual variation) and may motivate repeated use by an individual. Withdrawal symptoms may also motivate further use. Environmental and social stressors, especially in childhood and adolescence, clearly interact with individual neurobiology and, consequently, behaviour, and are thus important risk factors for drug abuse. Once the person has become addicted, factors such as physical, psychological and associated lifestyle changes, developmental delays because of drug abuse behaviour, secondary social difficulties and comorbid physical and psychiatric

disorders contribute to ongoing drug abuse (Volkow, 2004; Mohn et al, 2004; Rhee et al, 2003; Jacob et al, 2003).

Some of the complexities of drug-taking behaviour

Not all people use drugs for the same reasons, and even in the same person the motivation for drug use may vary, depending on the stage of addiction. There are a multitude of reasons why people would start taking drugs, and there are as many reasons why addicts will continue taking drugs. Some may desire intoxication rather than mere sobriety. The reason a young adolescent chooses to take his/her first heroin dose is vastly different to that of the heroin addict further down the road of addiction. Likewise, the motivation to use or not to use a substance during any of the different stages of recovery from substance dependence is complex, depending on the individual's motivation, thoughts, emotions, circumstances, lifestyle and physical neurocognitive status at the time.

To what extent are people predetermined products of their genetic make-up? The work of Volkov strongly suggests that there are individuals with a 'vulnerable' brain, waiting for the first dose of heroin (Volkow, 2004).

To what extent are adolescents vulnerable to drug use merely because of their age, the age during which they believe themselves to be omnipotent and to 'know it all'? How much are people driven by the situations in which they find themselves? How much of drug-taking behaviour is motivated simply by the drug's effect, and how much by trying to avoid the discomfort of drug withdrawal? Finally, how many addicts persist with their drug-taking behaviour due to secondary compromised cognitive function or because of a primary psychiatric disorder or psychiatric sequelae secondary to their continuous drugging?

Once addicted, addicts should be able to exercise personal choice and take responsibility for their illness if they have the emotional, cognitive and behavioural capacity to understand the illness, the burdens and benefits of ongoing drug-taking behaviour, the burdens and benefits of various treatment options and they have proactively been offered treatment services (White, 2008; Corrado, 1999; Oddie, 1993; Singer, 2000).

Complexities in the therapeutic relationships with addicts

Most patients suffering from physical illnesses are fully competent to understand their illness and the possible treatment regimes, and to ask for help. Not so patients suffering from serious psychiatric illnesses. Patients suffering from an acute psychotic illness, with poor reality testing, reacting to their delusions and hallucinations and exhibiting self-defeating, disorganised behaviour are clearly incompetent to understand their illness and treatment options and cannot decide in their own interest. There are other patients in whom the competency to make reasonable decisions in their best interest is partially compromised or unclear. Some addicts are such patients. Deciding whether to use a paternalistic or non-paternalistic therapist-patient interaction is a complex value decision that has to be made. This potential moral therapist-patient relationship dilemma makes it necessary to explore the everyday person-to-person interaction, dependence or independence or our social contract.

Human existence in our communities depends on relationships. Daily human interaction is about our connectedness, our 'making it work' and our synthesis. We are together, yet individual. We should respect one another, we should be free, we should celebrate differences, we should be autonomous beings, have the right to life, freedom, basic needs of life and be allowed to achieve and own by hard work. In our social contract we should always treat others as 'ends' in themselves and never as a means to an end. I should always treat others as I would like others to treat me. Discomfort may arise in a therapist when 'blind' respect for the autonomy and freedom of a person becomes a duty, even if that person by choice actively wills an action that clearly may seriously jeopardise his or her health or future wellbeing. Autonomy presumes that the person has the emotional, cognitive and behavioural tools on board to be able to make a 'rational person's' decision (rationality). Can the state of addiction render the addict 'incompetent' to make rational decisions? If so, should the therapist not care, or take the 'good' action by intervening? Our social contract is not clear. We have to make difficult value decisions.

With respect to the concept of freedom of choice, the following questions can be asked: are we really free to choose, or are all actions predetermined by personal history and experiences, genetic predisposition, future wishes or 'ends', the situation of the moment or the larger concept of determinism? Or are we free in the libertarian context where, given the same set of circumstances, a person can make divergent choices on different occasions? Again, does the illness of substance dependence render the person less rational?

In medicine, there is often conflict between the patient's right to autonomy and the doctor's duty to act in the patient's best interest. The complexities of what will be discussed here rest on this push-pull scenario of individual free will (or respect for autonomy) and the illness rendering the person incapable of rational decision making.

The therapist-patient relationship or roles has evolved through history. In earlier times, 'health carers' were less healers and more rightly 'sickbed attendants', trying to comfort and support those who were ill. One may argue that modern science has arguably made health carers effective healers but less effective comforters. Health carers are now considered professionals with the 'know-how', which may contribute to the fostering of paternalistic attitudes. As a rule, most patients cannot ever be on par with the scientific knowledge and skills of the modern-day health carer. The doctor-patient relationship, requiring shared responsibilities and interactions, poses a moral dilemma. Ideally, the relationship should be an equal partnership, but because of the disparity between the knowledge and skills of the patient and doctor, it becomes an 'unequal' one. Between the 'two parties', what are the rules, rights, duties or virtuous actions that would make this 'unequal' relationship 'equal', characterised by mutual respect and responsibility? For one, should the therapist ever become the mere 'agent' of the patient, yielding blindly to his or her needs and will? On the other hand, should the therapist dictate patient needs and the best action to be taken?

So far, several moral questions have been asked. Many difficulties may face the clinician involved in caring for an addict. The different motivational drives of the doctor (care) and patient (addiction) can lead to a chasm between the therapist (who possesses the knowledge and skills of the profession) and the patient (autonomous agent). Further tension can occur if the motives and needs of the family unit and the community are also brought to bear. Even the best healthcare provider with the best scientific knowledge available cannot achieve an

optimal result if the patient refuses to take ownership of his/her illness. These reflections on the doctor-patient relationship identify the following moral dilemmas for discussion:

- The very strong moral principle of respect for patient autonomy by the therapist, and the right of patients (addicts) to choose their own destiny, should form the essence of any moral discussion
- A second moral dilemma can also occur when the patient, by virtue of his or her illness, becomes 'incompetent' to make autonomous decisions. How does one judge patient (in this case, addict) competency to request, provide consent for, or refuse treatment?
- Furthermore, under certain circumstances, the behaviour, lifestyle and communal actions of addicts may be detrimental to the community, leading to a moral dilemma if they choose to exercise their right to autonomy and self-determination and refuse help. How much freedom of action by any individual can/should be allowed by the community? How much freedom can the addict claim from the community?

It becomes clear that moral dilemmas and difficult bioethical decisions are our everyday companions in medicine, particularly in the field of psychiatry, where the clinician is confronted with the complexities of human behaviour, thoughts, emotions, moods and interactions. At best, few individuals can claim unwavering 'harmony' or balance within themselves and with others. 'Illness' in the form of addiction has the potential to compromise human autonomy, freedom and the ability to act for one's own good. Therapists are trained to intervene in order to limit patient suffering. When asked for help, the health carer has a moral obligation to provide help. Also, at times a patient may request help that is deemed to be outside the therapist's professional duties or in conflict with good clinical practice: for example, patients asking for 'false' sick certificates clearly because of yesterday's alcohol abuse 'hangover'. Clinicians should always seek to balance patients' needs and wishes (demands) with the burdens of illness, the benefits and burdens of treatment, the best knowledge of science and what is regarded as best current clinical practice. At times, a clinician may confuse his/her eagerness to help with standing good clinical practice. The health carer should be able to build moral arguments and to deliberate on a difficult clinical ethical situation based on the individual circumstances and context.

In the Oath of Hippocrates we read, 'To the best of my ability and judgment'. Although Hippocrates started off by saying, 'I swear to Apollo', indicating a belief in some mythical god, it may be understood that what he meant by 'ability' would be the knowledge and skills of the day. By 'judgment' he acknowledges the fact that therapists must make those decisions (mainly value judgments) that are not obvious by medical scientific knowledge and skills alone. These judgment calls mostly pertain to bioethical decisions or doctor-patient interaction decisions. Our medical scientific knowledge and accompanying skills are vast, but are not complete. Our doctor-to-patient interaction (relationship) is much improved, but not complete. All healthcare workers are to some extent philosophers and are required to make judgment calls.

Healthcare workers, in their quest for doing what is 'good', occasionally have to ask difficult fundamental moral questions. These include metaphysical questions such as, 'How should I live my life in order to live a good life?', or 'When does life begin or end?', or 'How should I interact with others?', or 'Will science ever be able to secure the "final" answers

by way of a universal common language?' Until such time, we have no choice but to dwell in a world with many uncertainties. Healthcare workers need to learn to feel comfortable with uncertainties, especially uncertainties outside of science in the fields involving human interactions. In an attempt to create meaning and order, we are forced to make very difficult decisions in our field of doctor-patient interaction. Aristotle (488–432 BC) suggested that we should spend our lives in search of the good life. Therapists should strive to become 'good people'. He said that life is concerned more with *who we are* than *what we should do* (character).

In the field of addiction, we serve people whose chronic mental illnesses (substance dependence) have made them vulnerable in making good self-interest or healthy decisions pertaining to their own health and future. Our further moral deliberations mainly focus on patient competency, respect for patient autonomy, liberal individualism, standard of care, patient advocacy, beneficence, non-maleficence and what is fair (best) toward both the patient and the community. The question is, what is morally good and how does one develop good moral arguments that underlie good actions?

Standing rules, professional guidelines and legislation

Moral action is motivated by a combination of personal moral standards, community moral standards, traditional and cultural values, the rules and guidelines of the profession and the legislation and the constitution of a country (HPCSA, 2006; South Africa, 2002; South Africa, 1996). State legislation and the Constitution are largely the products of many years of history involving collective community consensus and/or the 'will of the nation'. But contemporary rules, guidelines and legislation are constantly being revised as new scientific and moral developments emerge. Current rules, guidelines and legislation may not necessarily guarantee moral good. For example, South Africa's Constitution and Bill of Rights clearly state that patients have a right to basic, good-quality health care. Yet clinicians are left to struggle with huge service demands and scarce resources that make such care difficult. Often, therapists have to make 'value-based' decisions, that is, to do not what is 'best' but to do what is best within a particular setting, given what is available and affordable at the time. The therapist must also make decisions on the basis of applicable Acts related to health, ethical guidelines of the Health Professions Council of South Africa (HPCSA) and clinical patient management protocols, all of which may not always give clear answers when needed.

Rules, guidelines and legislation do not render moral deliberations in patient care obsolete. At the best of times, clinical dilemmas may not be solved by merely adhering to the 'rules'. While rules are mostly made with the sole intent of doing good, they cannot stand alone in moral debate and cannot guide good moral action in all clinical situations. Within an 'imperfect' science, rules often do not stand the test of difficult clinical situations, and clinicians have to make 'judgment' calls that strive toward good action. To a large extent, everyday therapeutic actions and interactions are *directed* by our personal moral norms and only *guided* by our professional norms and standards and the Constitution and laws of our country. Most of these can coexist, but they may in certain situations also create moral conflict. Thus, personal (therapist) belief systems regarding the treatment

of patients with substance dependence, current legislation and professional norms and standards might be in serious conflict with one another. Healthcare workers' concepts of when a patient is competent to make autonomous decisions, or has a right to personal decision-making, may also be in serious conflict with what is considered right by non-clinicians. Again, it becomes clear that, within the discipline of health care, moral good life and action for the individual, the professional and the community at large are littered with different conceptualisations and moral conflicts. Every therapist should approach this with an attitude that compels him or her to strive to achieve the moral good, that is, a personal quest to do what is morally good.

Concepts, paradigms and belief systems

How do individuals come to 'know', ie, arrive at the personally held convictions that shape their attitudes and actions? From birth and through the developmental years, we experience our surroundings, interact with people, learn a language of communication and come to formulate individual concepts and belief systems. So too do clinicians 'make up their minds' and 'come to know'. However, in the healing profession, currently held personal concepts and paradigms repeatedly fail to help one decide on 'the good moral action'. What constitutes good moral action in a specific situation is often unclear. The healthcare worker, uncertain about how to proceed, must rethink the problem, challenge old ideas, examine all options, reflect and go back in search of the underlying fundamental values and truths. As therapists, we should nurture uncertainty, not be afraid of novel thinking, and not be scared of change if it is for the betterment of others. Warburton said: 'If I do not challenge the soundness of the concepts on which my life is based, I am impoverishing my life by not exercising the power of thought' (Warburton, 1999). Should a therapist 'know' and merely act on his/her set of opinions, and not engage in open-ended thinking and have the courage to ask questions, the action that might follow might not always represent what is morally good.

In the field of addiction treatment, an unwillingness to challenge old concepts may be the biggest obstacle to good moral (clinical) action. Contemporary medicine has changed from the paradigm of making every effort to cure illness and respect life as its only duty, to one that includes respect for patients' wishes, ideals, choices, future plans and quality of life. Although modern medicine advocates outcomes-based treatment regimes for addicts, can these treatment regimes be enforced? The fact that there are effective treatment modalities for addicts surely does not mean that all addicts must 'want' this treatment. The goals of the therapist have shifted from treatment and life at all costs to respecting human choices.

The construction of logical arguments

Before embarking on contemporary moral theories and how these theories should be utilised in moral deliberation in the doctor-patient interaction in addiction, the mere building of arguments should be reflected on. Communication in the world today is often beset with flawed arguments, clever plays on the meaning of words and emotional rhetoric. These are so blatant and widespread that the content (truth) of what is communicated is often unrecognisable.

Good moral arguments are built from facts, statements or propositions. These can be true or false and should be challenged for correctness. Several related facts, statements or propositions should, if put together rationally, lead to a conclusion. Facts, statements and propositions resulting in deductions and conclusions must be rational and correct in order to build a true argument. The next step is to evaluate whether the argument at hand is a factual argument, emotional argument or a moral argument.

A factual argument is the most persuasive, and the easiest to acknowledge as true or correct. For example: 'Cape Town has a sunny summer and a cold, wet winter.' An emotional argument, on the other hand, makes use of rhetoric to influence and persuade. Rhetoric is the use of words, language and emotions to build persuasive 'arguments'. For example: 'If you are loyal to your country, you should not consider leaving it.' Emotional arguments should be recognised and avoided, as they seldom lead to logical conclusions. Moral arguments are used when the question, situation and/or problem cannot be solved by mere facts alone. In putting forward a moral argument, all participants should be willing to listen, reflect, ask fundamental questions, rethink, challenge, adapt, change fixed concepts and be willing to, at the end, allow for change. One example of this is the following: 'You cannot discharge the alcohol-dependent patient from the hospital as the patient will go back to his alcohol abuse, and that poses a danger to self and others. You will be to blame if the patient develops liver failure or kills someone in a motor vehicle accident.' Although this argument puts forward some facts and surely plays on the hearer's emotions, there are some deeper value issues involved. Let us take a closer look at this argument:

- Statement 1: The patient is alcohol-dependent. (This can be tested as true or untrue.)
- Statement 2: The patient poses a danger to self and others. (This statement can also be weighed as true or untrue by experience.)
- Deduction: The patient should not be discharged.

In this case the statements are true, but the deduction does not follow logically as it does not take into account a multitude of unstated facts, the complexity of the clinical situation and the 'value' issues. Perhaps there are no beds available and other patients need more urgent attention. Here one needs to balance the conflicting needs of the patients requiring admission (value issue). It may be that the patient refuses further treatment (value issue). (Should the patient not be made an involuntary admission?) The patient may be incompetent to make any further decisions about treatment (value issue). Furthermore, the patient may refuse to take ownership of the illness – again, a value issue which bears on the argument conclusion and action to be taken. What about the right to choose and respect for autonomy? In this case there may also be a post-discharge plan of action in place. More value issues may arise in this case. Should therapists decide on who should be driving on our roads? In this case, therapists are trapped between two equally strong value issues: (1) the social and civil duty of the therapist to report a potentially dangerous driver on our roads, and (2) the duty of the therapist to uphold doctor-patient confidentiality (respect for patient autonomy). The doctor-patient relationship is built on the covenant of trust. If patients cannot trust their clinician, there can be no therapeutic relationship. On the other hand, doctors also have a civil and community responsibility. Lastly in this case, how does the often lengthy and complex therapist/patient motivational process fit into the decision to discharge/not to

discharge? In the case of value arguments, all parties must be willing to reconsider, think again and be open to new ideas and decisions.

To help with this judgment call, one can make use of contemporary moral theories. In the case of doctor-patient interaction, arguments often involve complex value considerations.

The theories of moral deliberation

The following case study illustrates a moral dilemma and the bioethical tools (theories) that may be used to argue and reflect on in sound moral deliberation.

Case study: A 36-year-old male nurse with a history of alcohol abuse and previous withdrawal convulsions repeatedly presents to his family doctor on Monday mornings smelling of alcohol and asking for a sick certificate. His alcohol abuse has been confirmed by physical examination and blood investigation. He minimises and rationalises his drinking habits, refusing any treatment. Motivational interviews have been unsuccessful, and even family involvement has not helped the patient to attain sobriety or reach a stage of acceptance. According to his wife, he regularly drives his car under the influence of alcohol.

Not obtaining a sick certificate could cost him his job at the hospital, with the family having to bear the brunt of what would follow. Since there is a history of withdrawal convulsions, it is clear that if he goes 'cold turkey' he will likely experience severe withdrawal. He has no other comorbid psychiatric disorder, often smells of alcohol when presenting at the surgery and always complains of vague somatic symptoms.

What should a good therapist do? Respect his autonomous decision to refuse help? Issue a sick certificate? If so, what should the diagnosis be? Should he be admitted as an involuntary patient and treated for his pending alcohol withdrawal? This is a very real problem that often arises in clinical practice.

Some of the questions that can be asked include: What action will yield the best result? If the doctor has the best interest of the patient at heart, what rule should he/she adhere to? What would most *good* health carers do? What and whose human rights are at play? If the community were to decide on the best action, what would they decide? If you were to take into consideration all the information at hand, and the individuals involved, what would you do? What would a caring person do, and how would you choose between respect for autonomy, beneficence, non-maleficence and what is fair or just?

There is no one clear answer to these questions. More importantly, these questions guide us to think, rethink, ask further questions, consult, struggle with value questions and make argued judgment calls. To build solid arguments when making difficult judgment calls, health carers who manage addicts should be well acquainted with the contemporary moral theories discussed below (Beauchamp & Childress, 1994; Kuhse & Singer, 1998).

Utilitarian ethics or consequentialism

Moral decisions should abide by the action that will ensure the best result for the most people in the long run. This action is aimed at maximising results. Indeed, a strong and

rational theory should be foremost in any moral deliberation. However, theory cannot stand alone, unchallenged. If utilitarian ethics are driven by 'best' results only, then the 'best result' should be carefully scrutinised. The therapist should also carefully consider the means to be taken toward achieving the 'best results', because the means (actions) may at times be inhumane and may not constitute good clinical practice within our profession. Utilitarian theories rightly consider 'most people', but in doing so may ignore the consequences of an action to the individual. The term 'the long run' is stipulated because the best result may, in many instances, be the quick, easy or short-term way out, but may ultimately not constitute the best decision. Useful questions for testing a chosen action and the long-term consequences of actions include: 'Can I always do this?' and 'Can everybody always carry out this action? Utilitarian theory is a useful and strong starting point in many moral arguments.

Deontology or rule-based ethics

Kant stated: 'we have the gift of thinking rationally.' Thus, since we have the powerful ability to think logically and rationally, we can make universal rules. Examples include: we should never kill, we should never lie, we should never break a promise. We have an intuitive ability to reason out and sense what is morally good. Rules should, however, respect the action of good intent. If, for conflicting arguments and complex situations, a rule should be disregarded, it may lead to the 'slippery slope' problematic. Soon it would become common practice to disregard that rule. The opposite may also be important, for in the real world good moral actions cannot be dictated by rules only. For example: in a situation of xenophobic violence I am hiding an immigrant in my house, fearing she might be killed. Armed, angry people knock at my door asking whether I am hiding any immigrants. The rule of truth-telling (or veracity) may be disregarded here.

Virtue-based ethics

Also referred to as character-based ethics, this regards moral action as being the action a good (or virtuous) (wo)man would take. To do the good thing only because it is good may be remarkably difficult. Human actions and interactions are frequently motivated by primary or secondary gain and not merely because they are good in themselves. How does one become a good person? Good role models, or 'wise' people in our lives, are people we can follow. Aristotle referred to human '*telos*', or human purpose. He believed that if we reached our true *telos*, we would have enjoyed a good life. This is a life in which happiness is experienced because the owner of that life constantly strives towards moral good. The only clear building block to virtue is to treat others as you would like others to treat you. Aristotle therefore said, 'The good life is spent in search of the good life.' To achieve this we must respect and love one another, and should strive towards morally good actions without the expectation of personal gain, a task that is truly difficult at best. Virtue cannot be taught and may elude many, yet a life spent in search of virtue would be considered a good life. Virtue ethics would give the therapist the opportunity to reflect on his/her own motivation towards actions, search for wise, virtuous role models, and have the courage to pursue that which is good.

Liberal individualism

Every individual has four basic rights: the right to life, freedom, basic needs (water, food, safety, health care etc) and ownership of property. Here, the emphasis is on the individual and not on the masses. History has taught us that the wishes of the masses always overpower those of the individual, prompting over time the laying down of these inalienable individual rights. The right to freedom also means the right to choose one's own treatment options and to participate in treatment programmes, but also the right to refuse treatment. Basic life needs include water, food, education, protection and health care (health care that is effective, outcomes-based, equitable, affordable and available for all). Every human right is balanced with the rights of the next individual and comes with responsibility and accountability. Rights cannot always be claimed by those who are entitled to them. It is the duty of every citizen and therapist to bestow rights on others, especially those who are not able to claim these rights (namely, children, demented patients, people with mental disorders and others).

Communitarianism

In a healthy community, people have common goals, which should serve the community. Communitarianism concerns the common good. If I were in a position to create a community, what characteristics would this community possess? I would naturally want to live in a community that nurtures diversity, finds common ground on issues of safety, financial growth and prosperity, and has respect for family values, culture and tradition. In any moral deliberation, one must respect one's community and its common good values. Harmful traditional practices also exist. If tradition no longer serves the common good, the community must have the will to challenge it. The aim is to strive towards what is *good*, but only if it *is* good, and as long as one can maintain respect for cultural diversity. How does addiction relate to the common good? If addiction causes individual and community suffering, then the community is likely to ask of the therapist, 'Can you treat this illness successfully?' If an addict's substance abuse is perceived to be a source of harm to the individual or the community, community members will be more likely to request effective interventions from therapists.

Ethics of care

As therapists, we have a duty to care, and to ensure that such care is equally distributed, effective, available, minimally invasive, affordable, complies with good clinical practice and, most of all, is accessible to everyone, including those who are unable to claim the right to care because of their illness. Care should, however, not be forced upon a competent person who refuses treatment. As therapists, our obligation to care for others may be comparable to the biblical parable of the Good Samaritan.

Casuistry or case-based ethics

Mistakes are often made because not all the information pertaining to a specific case or situation is taken into account. It is, therefore, very important to gather all relevant information necessary to make an informed decision. Most difficult moral decisions may become straightforward when all the facts are carefully considered. The next step is to

consider the outcome of similar previous cases and to draw on experience prior to making a final decision. This is an essential component of all moral deliberation.

Principle-based ethics

The four tenets of principle-based ethics are autonomy, beneficence, non-maleficence and justice.

Autonomy

Respect for autonomy (or self-determination) is the principle of allowing the patient to make his or her own decision after being given the relevant information and appropriate treatment options. This means that the good moral agent respects a 'wrong' decision made by a competent, fully informed patient. Experienced therapists, who may have witnessed devastating outcomes suffered as a result of patients having made the 'wrong' decisions, frequently find it hard to support such decisions, and in consequence may tend to react with paternalism.

Nevertheless, bad decisions can have catastrophic results, not only for the decision maker but also for the community. Failure to prevent an intoxicated person from driving a vehicle has been the cause of numerous tragedies. Again, the clinician is faced with 'value' decisions in which a patient's right to autonomy may conflict with the common good and patient confidentiality.

Autonomy protects patient privacy and confidentiality. Privacy means non-intrusion into patient values, wishes and needs, and confidentiality means not divulging personal patient information. In the field of substance abuse treatment, respect for patient autonomy and the patient's motivation to take ownership of the illness is of the utmost importance. Problems arise when the patient is not fully competent to make decisions in his/her best interest.

Beneficence

This is any action that will benefit the patient. Mere patient choice could harm the patient, thus does not always constitute a beneficent action. With regard to treatment outcome, the patient should benefit from the experience after weighing and balancing the benefits and burdens of their choice of treatment. The clinician's action should also fall within the scope of good practice.

Non-maleficence

This means not to (ever) harm the patient, that is, to always put patients' needs, wishes and wellbeing first. Again and again, especially in the cases of the rationalising, intellectualising, projecting, minimising and denying addict, clinicians may be confronted with patients making 'wrong' decisions. The interplay is between respect for patient autonomy versus beneficence or non-maleficence.

Justice

This refers to what the fair action would be – action that is fair both for patients *and* for others. To judge what is 'fair' in a specific situation entails having to balance arguments, outcomes, harms and gains, and to do what a reasonable person would do. As a result judgment calls are inevitable, and the therapist should learn to use the above moral theories

daily as instruments of moral deliberation, avoid making decisions in isolation, and always rethink old concepts and existing paradigms.

Balancing morality

In evaluating the above theories and principles, it is clear that no single moral theory can stand alone. There are conflicts between theories and within theories. Weighing and balancing concepts is inevitable in moral decision-making, and therefore all the theories and principles described above must be brought into play.

In order to illustrate the use of the eight moral theories in clinical decision-making, let us return to the case study involving the alcohol-dependent patient. Should the patient be treated against his will? There are arguments in favour of treating and arguments against treating such patients:

- **In favour of treatment:** If alcohol dependency is a disease that can be successfully treated, then weighing the burden of treatment against the benefits of treatment leads one to the conclusion that the *best result* would be obtained by treating the patient. It would also be the action of *good intent*. The burden of treatment (means to the end) cannot be considered inhumane. It would also be the *virtuous* action: the patient has a right to basic good care. Treatment will favour the *common good* of communities; it would also be, in accordance with *experience*, the *caring* thing to do in *this case*. The patient would *benefit* from treatment and his autonomy could be restored.
- **Against the action of treatment:** The therapist should respect the patient's *autonomy*, his *right* to refuse treatment, and not cause *harm* by involuntary treatment.

The therapist should now weigh and balance the arguments and make a decision that will be *fair* towards the patient, the family and community. If the patient were fully competent, only mildly intoxicated and not in withdrawal, one would certainly want to respect autonomy and the right to refuse treatment. If the patient is in withdrawal, with a history of complicated withdrawal, the burden of treatment is surely not worse than the illness itself. In this case, there is the fact that the intoxicated patient is going to drive home. Should he go into a state of withdrawal without the necessary care, serious harm could follow. The therapist should reconsider the arguments *for* treatment even if it would mean suspending autonomy for the period of treatment (ie. involuntary treatment). It may be the virtuous action to treat the patient as an involuntary patient temporarily and in the process restore competency and the right to make competent willful rational decisions.

The above scenario clearly demonstrates that contemporary theories cannot give final answers to today's moral debates, but may pave the way to developing well-considered arguments. During the final weighting and balancing process, all deliberating parties should be open and willing to adapt, rethink and move a little bit closer to what could be considered the final moral good in that situation.

How can one help the therapist and achieve maximum outcomes for the addicted patient in such a difficult clinical situation? The therapist would be advised not to act in isolation, but to consult and seek help from his or her peers, while reflecting on the balance between his or her own need to care and respect for the patient's right to self-determination. The South African Mental Health Care Act, 17 of 2002 (MHCA) and the Prevention of and

Treatment for Substance Abuse Act, 70 of 2008 (South Africa, 2002; 2008) make provision for lawful actions that could be carried out in such a case. Consider the example of a 56-year-old bus driver with severe alcohol withdrawal, liver failure and threats of violence towards his family who refuses admission for detoxification. He could be admitted as an involuntary patient because (1) he has a serious psychiatric disorder, (2) is a danger to self and others, (3) refuses treatment and (4) can be treated.

In everyday clinical practice, the doctor-patient relationship is voluntary and initiated by the patient (need). At times, and because of patient (in)competency to make a reasonable person's decision, the health carer has to rely on health legislation (in this case the MHCA) to be able to foster clinical action. Current legislation is the result of many revisions that have occurred over an extended period of time, in response to the wishes, needs and deliberations of society. Legislation regarding the management of patients with substance dependence is thus a final product of the consensus reached by the community. Would acting in accordance with the MHCA necessarily make the clinical action a good moral action?

Legislation may aid the clinician in his or her decisions, but it cannot be considered to have the final say in what constitutes good or moral action. For example, admitting a patient as an 'involuntary' patient under the MHCA or by means of a court order would legitimise the therapist's action of taking away that patient's autonomy, but it does not guide the therapist as to when, and in what exact situation, he or she should make use of the Act. Furthermore, legislation is constantly being revised, and cannot therefore be relied on to give the final answers.

The role of patient competency

The essence of the philosophical, moral and bioethical debate is whether some addicts, because of their illness, become incompetent to make a 'reasonable person's' decision. If so, when do they cross that point? If an 'incompetent' addict were to refuse treatment, it may be 'good' to intervene and commence or enforce appropriate treatment. How far should the community allow the 'incompetent' addict to make what most would consider wrong and self-defeating choices? If the therapist was to intervene, it might be construed as being morally wrong (ie, misguided paternalism). One solution would be to allow 'incompetent' persons to claim their rights as far as possible (ie, where it would be safe to do so), and to intervene only in the event of 'imminent' danger to themselves or others. Judgment of imminent danger by clinicians can be very difficult and notoriously inaccurate. As an example, consider the danger an intoxicated driver poses to the community. If a patient is deemed incompetent, that person would be considered as having the right to life-saving treatment. Moral progress in society will have occurred when it has become less necessary for an individual to claim his/her rights, because the community at large has learned to bestow these rights on all, even those who have the right to involuntary treatment. This is an especially important issue in both the vulnerable psychiatric patient and the addict.

In patients with alcohol dependence, the question of competency to make informed decisions can arise. Can the illness of substance dependence cause the patient to become incompetent? During the end stage of illness, incompetency or the inability to make

informed decisions may be obvious, and may not pose a serious moral dilemma. A more difficult dilemma arises if subtle early cognitive deficits that are difficult to quantify confer a 'degree' of incompetency. Patient competency (the cognitive and emotional capacity to make an informed 'best interest' decision) is not an all-or-nothing situation in that patients can exhibit degrees of competency.

Beauchamp and Childress (1994) suggest seven 'levels' of competency:

1. The patient can communicate a decision (understanding, insight and judgment not evaluated)
2. The patient can communicate and understand immediate facts and consequences of a decision
3. The patient can also understand relevant facts and information about the illness and its treatment
4. The patient can build arguments
5. The patient can build rational arguments (which can be tested and contested)
6. The patient can build burden-benefit or pros-and-cons arguments
7. The patient can make a reasonable person's decision.

If patient competency is to a 'degree', then who would be competent to make a treatment decision? If a patient needs to decide on a minor issue like breakfast preference, then surely even someone at Level 1 would be 'competent' to make that decision. If a decision is a serious one and has major impact on the wellbeing of a patient, one could argue that patient should at least be at Level 5 or 6 to make such a decision. Thus it is not only the level of competency, but also the weight of the decision and the gravity of outcome of that decision. In terms of gravity, one should consider the burden of illness and treatment, the treatability of illness, the benefit of treatment, the potential success of treatment and the impact of the illness on the patient's family and community. As far as possible, the therapist should respect human rights and patient autonomy, even for the incompetent patient, until such time that the benefit/burden principle indicates that treatment outweighs respect for autonomy and the right to refuse treatment. If the patient is incompetent and the disorder is reversible by virtue of treatment, and the treatment is humane, one can argue that the patient should have the right to such care. In psychiatric practice, therapists are often confronted with severely disordered patients who cannot make informed decisions and who cannot act in their best interest on account of illness. It may be argued that it would be the moral good thing to temporarily suspend self-determination and treat the patient through the consent of surrogate decision-makers (closest family) or involuntarily for the sole purpose of restoring competency and good health, if this seems possible.

Informed consent

Allowing patients to take 'ownership' of their illness, and to become partners in the recovery process, requires us to inform them about the illness and the available treatment options. According to Beauchamp and Childress (1994), there are three elements of informed consent:

1. **Threshold elements**
    - Competence (to understand and to have the ability to decide)
    - Freedom of choice

2. **Information elements**
   - The provision of necessary information
   - Recommendations
   - Comprehension of the information and recommendations
3. **Consent elements**
   - Own choice
   - Provision of consent to implement the decision

Freedom of choice means freedom from any coercion. The patient must choose the intervention without being influenced by threats, manipulation, promises, emotional pressure and half-truths. Consent that is reluctant, half-hearted, pressurised or unwillingly given can be strongly contested. Forms of consent that are not defensible in a court of law include: the silence of the patient; the doctor 'assumed' that the patient gave consent; it was a 'routine' procedure; the patient 'did not refuse'.

Information must be key information. It must be unbiased, impartial, not loaded and comprehensive enough to permit a decision. It must be communicated in simple, understandable language, preferably in the patient's home language, and be age-, culture- and religion-appropriate.

Recommendations must be outcomes-based and only in the patient's best interest. Recommendations must not be motivated by financial gain on the part of the doctor, and the doctor must not be under obligation to any party other than the patient.

The decision must be the patient's own choice. The patient, after consenting to a course of action, should also be allowed to withdraw such consent. The patient must show an appropriate level of competence in order to make rational choices. It represents the patient's ability to deal with informed consent in a rational way in the furtherance of his or her own best interest, and to convey his or her chosen decision as a free agent.

In patients with substance dependence, competency may be compromised by many interacting and well-known factors like drug intoxication, cognitive deficits caused by continued abuse, patients trapped in their socio-drugging environment, and culture (South Africa, 2008; De Bellis et al, 2000; Rogers & Robins, 2001). A 'value' dilemma can arise when an addict's deteriorating cognitive functioning, emotional state and personal drive become so significant (ie, cause harm to self and others) that the therapist believes that respect for autonomy should be temporarily suspended in order to treat the patient and restore competency. This decision is often further complicated by the number of interested parties – with vastly different motivations and incentives – that are involved and may exert pressure on the therapist to act in a certain way. These may include the patient, the family, the therapist and the larger community.

It may be asked: why do most addicts rationalise, intellectualise, minimise, deny and use projection to continue their drug-taking behaviour? Continued drug-taking behaviour by the patient may be motivated (driven) by:

- The direct drug effect, wanting or craving the drug effect (intoxication)
- The unknown sober lifestyle and known lifestyle of addiction
- Holding onto the only peers that give them some feeling of belonging

- The need to maintain 'self', and not to succumb to the stigma of addiction and the loss of control of their lives
- The psychological and physical discomfort of substance withdrawal.

The ability or desire to take ownership of the illness may be further hampered by presence of subtle cognitive, emotional and personality (drive) deficits caused by the substance itself (South Africa, 2008; De Bellis et al, 2000; Rogers & Robins, 2001). One may regard the addict as being trapped within the illness, trapped to such an extent that a therapist might contend that the patient's personal autonomy should be suspended temporarily. The opposite may be argued as well. The question should be asked whether, in contemporary moral debate, respect for autonomy should be regarded as a 'perfect' moral obligation. A 'perfect' moral obligation can be seen as a 'must' moral duty that would take preference over principles such as beneficence, non-maleficence and social justice. Until such insight is achieved, respect for autonomy should be balanced with patient and social beneficence, non-maleficence and justice.

Owing to the complexities of these value arguments, it is vitally important that more then one 'moral' agent be charged with making decisions on behalf of patients. Ideally, a panel of decision-makers should be employed.

Good moral action requires interaction and consultation with other people in the addict's life. Other individuals, especially family members, should be encouraged to enter into a partnership with the addict and the therapist. The family may be motivated by their connectedness, love, care and, possibly, mutual suffering. Family members are seldom informed about the illness of addiction, and often do not understand the full bio-psycho-social aspects of the illness or the person trapped within this illness. Therapists may be pressured by ill-informed or ignorant family members to take strong action. In such a situation, the family should be informed of the biological and psychological character of addiction, the necessity of weighing and balancing the needs, rights and autonomy of the patient with those of the family, the processes involved in motivating such patients, and the confidential nature of the doctor-patient relationship. The therapist should strive towards making the family part of the network of motivation towards future action.

The well-described condition of co-dependency is often found in families of addicts. A co-dependent family member may inadvertently enable the addict to continue the addictive behaviour by preventing its negative consequences or opposing efforts to treat the patient. It would be beneficial if co-dependency and the related phenomenon of 'enabling' could be managed within a 'network' consisting of therapist, patient and family members.

The next 'partner' to be considered is the community (identifiable individuals within the community and the community at large). The larger community represents a whole spectrum of ignorant, overprotective, inimical, suffering, guilt ridden, angry, helpless and co-dependent victims of the illness. The community members who are 'spectators' of the illness often have the attitude either that the therapist should 'do something' or that the addict should 'just stop'. This does not contribute constructively to the moral debate and may lead to paternalism by health professionals. Again, the therapist should provide

information and participate in open debate on the best treatment options and outcomes based on the evidence.

Conclusion

Ultimately, therapists know that science alone cannot heal the addict. In contemporary, everyday, health-related dilemmas we are forced to make extremely difficult clinical and moral decisions, yet in our patient-therapist relationships the *final* morally good action often eludes us. Addiction is a chronic relapsing neuropsychiatric disorder. At some stage in the life of an addict, the community should recognise the fact that the person is 'trapped' within his/her illness. The illness renders the patient incompetent to make a reasonable person's decision. It may be the truly virtuous action or good moral action to suspend the autonomy of the addict temporarily in order to grant the addict treatment opportunity, restore competency and regain autonomy. Therapists should never become isolated in their struggle to find answers. Therapists should nurture their uncertainty, knowing that at this moment in time the final moral 'social contract' (patient-doctor relationship) eludes them. This situation leads to a lifelong search for what is truly good. The only clue in this search is 'to treat others as we would like others to treat us'. Therapists have to do this with integrity and compassion, so that they can be trusted by patients and the community alike to act in their best interests. This means to serve and treat patients as ends in themselves and never as a means to an end.

References

Beauchamp, T.L. & Childress, J.F. (1994). *Principles of Biomedical Ethics*. 4th edition. Oxford: Oxford University Press

Brown, S.A., Tapert, S.F., Granholm, E. & Delis, D.C. (2000). Neurocognitive functioning of adolescents: effects of protracted alcohol use. *Alcoholism: Clinical and Experimental Research*, 24(2):164–71.

Corrado, M.L. (1999). Addiction and responsibility: an introduction. *Law and Philosophy*, 18(6):579–88.

De Bellis, M.D., Clark, D.B., Beers, S.R., Soloff, P.H., Boring, A.M., Hall, J., Kersh, A. & Keshavan, M.S. (2000). Hippocampal volume in adolescent-onset alcohol use disorders. *American Journal of Psychiatry*, 157(5):737–44.

Health Professions Council of South Africa, Professional Guidelines, Ethical Rules of Conduct for Practitioners Registered under the Health Professionals Act, 1974. *Government Gazette*, 4 August 2006. Available from www.hpcsa.co.za/; accessed 2 August 2011.

Huxley, A. (1951). *The Doors of Perception*. London: Penguin.

Jacob, T, Jacob, T., Waterman, B., Heath, A., True, W., Bucholz, K.K., Haber, R., Scherrer, J. & Fu, Q. (2003). Genetic and environmental effects on offspring alcoholism. *Archives of General Psychiatry*, 60, :1265–71.

Kuhse, H. & Singer, P. (eds) (1998). *A Companion to Bioethics*. Oxford: Blackwell Publishers.

Marks, J. (1996). Preventing drug mis-use. Psychiatry online 1(7):Paper 2, Version 1.1.

Mohn, A.R., Yao, W.-D. & Caron, M.G. (2004). Genetic and genomic approaches to reward and addiction. *Neuropharmacology*, 47(Suppl. 1):101–10.

Oddie, G. (1993). Addiction and the value of freedom. *Bioethics*, 7(5):373–401.

Rhee, S.H., Hewitt, J.K., Young, S.E., Corley, R.P., Crowley, T.J. & Stallings, M.C. (2003). Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Archives of General Psychiatry*, 60(12):1256–63.

Rogers, R.D. & Robbins, T.W. (2001). Investigating the neurocognitive deficits associated with chronic drug misuse. *Current Opinion in Neurobiology*, 11(2):250–57.

Singer, P. (2000). *A Companion to Ethics*. Oxford: Blackwell Publishers; chapters 35, 39, 40, 47.

South Africa (Republic (1996). Constitution of the Republic of South Africa, Act 108 of 1996. Chapter 2: Bill of Rights. Available from: www.polity.org.za/govdocs/constitution/saconst.html; accessed 4 July 2011.

South Africa (Republic) (2002). Mental Health Care Act, 17 of 2002. Available from www.acts.co.za/mhc_act/mental_health_care_act_2002.htm; accessed 4 July 2011.

South Africa (Republic) (2008). Prevention of and Treatment for Substance Abuse Act, 70 of 2008. Available from www.info.gov.za; accessed 1 December 2011.

Volkow, N.D. (2004). Imaging the addicted brain: from molecules to behavior. *The Journal of Nuclear Medicine*, 45(11):13–24.

Warburton, N. (1999). *Philosophy: The Basics*. 3rd edition. New York: Routledge.

White, W. (2008). Toward a philosophy of choice: a new era of addiction treatment. *Counselor*, 9(1):38–43.

18 Clinical treatment of substance use disorders in South Africa

Henk Temmingh and Bronwyn Myers

Introduction

Substance abuse treatment refers to the provision of specialised medical, psychiatric and psycho-social services to individuals with substance abuse and dependence disorders. Depending on the model used, the goals of treatment include enabling clients to abstain from or reduce substance use and to reverse the negative health and social consequences associated with substance use (Myers et al, 2008). This chapter reviews evidence-based pharmacotherapy and psychotherapy approaches to treating substance use disorders and describes the extent to which these approaches are used in South Africa.

Substance abuse treatment in South Africa

Historical development of treatment services in South Africa

Prior to South Africa's first democratic elections in 1994, treatment for substance use disorders was limited. This was true for all population groups, but especially for black South Africans who were disadvantaged during the apartheid regime (Myers, Louw & Fakier, 2008). Several socio-political factors hampered access to treatment for South Africans. First, state-subsidised services were inadequate and services poorly distributed. Most services were concentrated in urban areas historically reserved for whites, and there were major disparities in the availability and quality of service provision to black communities when compared with those for relatively more privileged white communities (Parry, 1997; Parry & Bennetts, 1998). Second, there was a lack of intersectoral collaboration on substance-related issues at the national, provincial and local levels between the Department of Health (DOH) and the Department of Social Development (DOSD). Through the apartheid years, these departments shared responsibility for the treatment and management of substance-related problems. For instance, the DOH was responsible for medical and mental health treatment and custodial inpatient care and the DOSD was responsible for prevention and community rehabilitation services. This division affected service delivery, as these sectors worked in isolation and neither took responsibility for local service delivery (Parry, 1997). Third, within these departments, the provision of substance abuse services was fragmented. This was partly due to the apartheid legacy of separate health and social welfare departments for each racially defined population group, which, when combined with their failure to work collaboratively to deliver treatment services, resulted in service duplication and poor distribution of services (Parry, 1997).

Since the country's transition to democracy, the state health and social welfare sectors have tried to tackle these service delivery challenges. The numerous social welfare departments have been integrated into a single structure to streamline service delivery, and the DOSD has been made the lead department responsible for substance abuse treatment (although the DOH remains responsible for medical detoxification and mental health services). Improving access to and the quality of treatment also has become a priority of the DOSD (National Department of Social Development, 1997), which has worked to develop a clear policy framework for addressing these issues. This policy framework prioritises improving service provision and includes a National Drug Master Plan and the Prevention of and Treatment for Substance Abuse Act, 70 of 2008.

Current state of substance abuse treatment in South Africa

Overall, around 10 000 substance abuse treatment slots are available on an annual basis, the majority of which are located in Gauteng and the Western Cape provinces, with fewer slots available in the rural provinces (Table 18.1). This is grossly inadequate, given that the South African Demographic and Health Survey and the South African Stress and Health Survey estimate that at least 10% of the South African population meet criteria for alcohol abuse and/or dependence disorders (Parry et al., 2005) and that 13% have a lifetime substance use disorder diagnosis (Herman et al, 2009). Although the number of treatment slots has increased since 1994, the bulk of these slots are located in the private for-profit treatment sector (Myers, Louw & Fakier, 2008). These facilities are unaffordable to the majority of the population who are without health insurance. For this sector of the population, the availability of affordable treatment has stagnated or decreased in recent years, as some large state facilities (which offered free treatment services) have closed. In

Table 18.1: Distribution of treatment services by province, 2009*

Region	Number of treatment services	Approximate number of treatment slots	Inpatient N (%)	Outpatient N (%)
Gauteng	32	3 200	21 (66%)	11 (44%)
KwaZulu-Natal	23	1 800	16 (70%)	7 (30%)
Eastern Cape	7	630	4 (57%)	3 (43%)
North West	1	150	1 (100 %)	0 (0%)
Free State	7	350	3 (43%)	4 (57%)
Limpopo	2	420	0 (0%)	2 (100%)
Northern Cape	2	190	0 (0%)	2 (100%)
Mpumalanga	3	300	1 (33%)	2 (67%)
Western Cape	32	3 000	17 (53%)	15 (47%)
Overall	109	10 040	63 (58%)	46 (42%)

* Extracted from audits of treatment facilities (Fakier & Myers, 2008) and the South African Community Epidemiology Network on Drug Use project (Plüddemann et al, 2009).

addition, state funding to the relatively affordable non-profit treatment sector has not kept pace with treatment demand, restricting the number of people that can be served (Myers, Louw & Fakier, 2008; Myers & Parry, 2005).

In South Africa, substance abuse treatment occurs in either inpatient or outpatient settings. Inpatient services are services where the client resides in a controlled drug-free environment for the duration of the programme. These services are indicated for clients experiencing withdrawal, with untreated health or mental health problems, who do not have a supportive family network or social environment, and who have chronic problems and previous failed outpatient treatment episodes (Gossop, 2006; Myers et al, 2008). In 2009, inpatient treatment was provided by approximately 63 facilities (see Table 18.1). These programmes range from short (21–28 days), medium (up to three months) to long-term (greater than three months).

In contrast, outpatient services provide non-residential services which are less intensive and restrictive than inpatient programmes, as they allow clients to return to their usual living environment after each session. Individuals thus continue with their employment, education and family responsibilities (Myers et al, 2008). Outpatient services are indicated for clients for whom withdrawal can be safely managed in outpatient settings, with stable health and mental health conditions, who are willing to participate in treatment, who have a supportive social network, and who do not have multiple failed treatment attempts (Gossop, 2006). In 2009, there were approximately 46 outpatient services available in the country, several of which had multiple sites. While outpatient services in South Africa are sometimes attached to inpatient facilities, they are more often found as stand-alone services within local communities. In this instance, they are referred to as community-based treatment services. These services vary in the intensity of care they provide: some programmes offer intensive services where the client attends the programme three to five times per week; others offer less intensive programmes where the person attends the service only once a week.

Apart from service availability, another challenge to effective service delivery in South Africa is concern about treatment service quality (Myers, Burnhams & Fakier 2010; Myers Fakier & Louw, 2009). One indicator of service quality is the degree to which evidence-based guidelines are implemented in treatment settings.

Evidence-based guidelines for substance abuse treatment

Evidence-based practices refer to practices for which there is a large body of research supporting their effectiveness. A practice is perceived to be evidence-based when: (1) randomised clinical trials have shown the practice to be effective; (2) effectiveness has been demonstrated in several research studies using different population groups and across different contexts; (3) the practice has a good effect on substance use outcomes; (4) the practice is based on a well-articulated theory of behaviour change; (5) the practice can be evaluated (Miller, 2009).

1. There are evidence-based guidelines for substance abuse treatment (see Box 18.1 for Summary). The first guideline applies because each individual has a unique set of problems and service needs, no single treatment approach is suitable for everyone. Treatment settings and services should be matched to each person's particular needs (McGovern & Carroll; 2003; Miller 2009; UNODC/WHO, 2008). In South Africa,

Box 18.1: Evidence-based guidelines for the effective treatment of substance use disorders

- No single treatment approach is suitable for all individuals
- Effective treatment is available, affordable and accessible
- Effective treatment addresses the multiple service needs of the individual and not just their substance use
- Effective treatment addresses co-occurring substance use and mental disorders in an integrated manner
- For treatment to be effective, it needs to be of a sufficient duration (90 days)
- Counselling and behaviour therapies are an essential part of effective treatment
- Medications are a vital part of effective treatment when used as part of a comprehensive treatment package
- Medical detoxification is a necessary first step in the treatment process for some, but by itself does little to change behaviour
- Possible substance use during treatment should be routinely monitored
- Effective treatment provides clients with access to HIV and other infectious disease services
- Effective treatment emphasises the importance of continuing care services as a means of avoiding relapse.

client-service matching generally does not occur. This is largely due to the limited availability and restricted range of services in the country. For example, the limited availability of affordable inpatient services often results in clients with high levels of problem severity (best suited to inpatient services) receiving lower-intensity outpatient services (Myers, 2007).

2. Related to this, the second guideline advises that substance use disorders are treated effectively only when people have access to affordable services in a timely manner (McGovern & Carroll, 2003; UNODC/WHO, 2008). Avoiding lengthy waiting periods for treatment places is important, as individuals are often ambivalent about entering treatment, and a treatment opportunity may be lost if treatment is not readily accessible (Myers, 2007). Therefore it is important to minimise barriers that restrict access to treatment. In South Africa, multiple structural barriers to treatment access have been identified. A case-control study of 989 persons with substance dependence from disadvantaged communities in the Western Cape identified geographic access barriers (such as travel time and distance to treatment), limited awareness of where, when and how to access services; affordability, poor quality of services, and lengthy waiting periods for treatment slots as powerful obstacles to treatment access (Myers, 2007; Myers, Fakier & Louw, 2009; Myers, Louw & Fakier, 2008). Three key interventions that may assist in limiting these barriers include: using treatment mapping tools to ensure the efficient allocation of treatment resources relative to service need; improving the availability of affordable services and limiting geographic access barriers by using mobile outpatient clinics as a mode of service delivery; and introducing a standardised performance monitoring system into treatment services to drive quality assurance and improvement programmes, thereby addressing concerns about service quality.

3. Because most individuals with substance use disorders have multiple service needs that cannot be addressed through substance abuse treatment alone, the third guideline is that effective treatment addresses the multiple service needs of clients (McGovern & Carroll, 2003; UNODC/WHO, 2008). These service needs may include the need for additional health services, due to the high prevalence of health problems associated with substance use; psychiatric care, due to the high prevalence of co-occurring mental disorders; vocational training and education services; family services (including parenting skills); and the need for legal services. When these multiple needs are not addressed, the risk for relapse is high (McGovern & Carroll, 2003; Gossop, 2006).

   To ensure this evidence-based principle is followed, it is essential to assess and address the client's service needs across multiple domains. While it is not always feasible to provide a broad range of services, service providers can still meet their clients' multiple needs through developing integrated care pathways (ICPs) (Myers, Louw & Fakier, 2008). ICPs are networks of local service providers in the substance abuse and health, mental health, vocational training, and family support fields that are contracted to provide specific services to clients where required (Gossop 2006). These networks ensure that clients receive the services they need while limiting the costs for service providers (Myers Louw & Fakier 2008).
4. Effective treatment ensures that clients with co-occurring mental disorders have their substance use and other mental disorders treated in an integrated manner (McGovern & Carroll; 2003; Miller, 2009). This is important because of the high prevalence of co-occurring disorders among substance users, and also because individuals with co-occurring mental disorders have more complex, severe and chronic problems, greater functional impairment, and poorer treatment outcomes than those with a substance use disorder alone (Craig et al, 2008; Grella & Stein, 2006; Padgett et al, 2008). Assessing clients for the presence of co-occurring mental disorders, and providing access to treatment for these conditions, improves the chances of recovery (Craig et al, 2008). Yet substance abuse treatment programmes in South Africa generally do not provide clients with access to mental health services. Audits of treatment services in KwaZulu-Natal and Gauteng provinces found that less than a quarter of services provide clients with access to mental health services (Myers & Fakier, 2009). This service gap raises questions about the effectiveness of treatment, and highlights the need to improve access to mental health treatment within substance abuse services as a matter of urgency. Where it is not possible to provide direct on-site access to mental health services, indirect access can be provided through referring clients to external agencies. In such cases, an active case management approach which ensures that clients are linked to external service providers should be adopted (Blakely & Dziadozs, 2008). Greater cooperation and collaboration between the DOH (responsible for mental health services) and the DOSD (responsible for substance abuse services) around service delivery also would assist in the provision of integrated mental health and substance abuse care (Myers & Fakier, 2009).
5. For treatment to be effective, the client also needs to remain in treatment for an adequate period of time. For clients with substance dependence, the length of time

spent in treatment is the single most consistent predictor of positive treatment outcomes (Gossop et al, 2002; Hser et al, 2004; Simpson, 2004). While the appropriate duration of substance abuse treatment depends on the individual's needs, 90 days is the minimum period required for significant improvement (McGovern & Carroll, 2003; Miller, 2009). After this, additional time spent in treatment may produce further progress (Gossop, 2006; NIDA, 1999). The length of time South Africans spend in substance abuse treatment appears far below the recommended minimum. One study found that on average clients spend about 31 days in some form of treatment, a third of the recommended time (Pasche, Myers & Adams, in press). This raises questions about the effectiveness of treatment in South Africa and highlights the need to improve clients' length of stay in treatment. This can be achieved through utilising stepped-down care approaches, in which clients graduate from higher-intensity to lower-intensity services over time. For example, a client may enter a short-term (21-day) inpatient programme, after which s/he may move to intensive outpatient services for 60 days or more and then graduate to lower-intensity outpatient services for several months. In addition, length of stay in treatment may be improved by encouraging clients to participate in abstinence-oriented, self-help support groups following a formal treatment episode (Pasche, Myers & Adams, in press).

6. Counselling and therapies targeting behaviour change are another essential component of effective substance abuse treatment (McGovern & Carroll, 2003; NIDA, 1999; UNODC/WHO, 2008). Over the past 30 years, many of the psycho-social treatment models for substance dependence have been evaluated, and several meet the criteria for evidence-based treatment approaches (Miller, 2009; NIDA, 1999; UNODC/WHO, 2008). Four of these approaches are described in the section on psychosocial models of treatment.
7. The seventh evidence-based guideline is that medication is a vital part of effective treatment for many patients (Gossop, 2006; McGovern & Carroll, 2003). Used during the course of substance abuse treatment, appropriate medication may facilitate engagement and retention in treatment by easing some of the physical and psychiatric symptoms of withdrawal that make it difficult for people to remain abstinent (Gossop, 2006). Opioid substitution therapy is an especially effective way of assisting those who are dependent on opioids to achieve abstinence (Gossop, 2006). However, recent audits of substance abuse treatment services in South Africa found that less than 5% of services provide clients with opioid substitution medications (Myers, in press). While access to effective substitution medications needs to be improved urgently, it is important to note that the use of medication is only really effective in the long term, when used in combination with effective psycho-social interventions (McGovern & Carroll, 2003; NIDA 1999). The multiple uses of medication are described at length in the section on pharmacotherapeutic management of substance use disorders.
8. Although medical detoxification from substances is necessary for some individuals, it is only the first stage of treatment and by itself does little to change chronic substance use (McGovern & Carroll, 2003; NIDA, 1999). Medically supervised detoxification, which safely manages the acute physical symptoms of withdrawal associated with

the cessation of persistent substance use, is a prerequisite for individuals who are dependent on alcohol, opiates, benzodiazepines, barbiturates and other sedative/hypnotic substances, as these individuals are more likely to experience high levels of discomfort or complications during the withdrawal process (Kleber, 1996; Mattick & Hall, 1996; UNODC/WHO, 2008). Yet medical detoxification services remain difficult to access in South Africa, with just over half of substance abuse treatment facilities providing any form of detoxification service (Myers, 2010; Myers & Fakier, 2007). This is mainly due to the lack of suitably qualified medical personnel within substance abuse services (Fakier & Myers, 2008; Myers & Fakier, 2007). Regardless of the reason for this finding, access to detoxification services needs to be improved, as, for many people, detoxification is a necessary first step in the treatment process (Myers, 2007).

9. Objective monitoring of a client's substance use during treatment should occur regularly as lapses back to substance use may occur during the course of treatment (Gossop, 2006; McGovern & Carroll, 2003). This is important, as evidence of substance use during treatment indicates that the treatment programme is not working for the client and requires adjusting. However, recent audits of South African treatment services reported that less than half of the services surveyed reported routinely monitoring their clients' substance use during treatment (Myers, Burnhams & Fakier, 2010). To address this service gap, treatment services should strive to test their clients' urine for the presence of drugs on a weekly basis. Clients should be tested for the broad range of substances, as it is not uncommon for clients to replace the use of one drug (eg, heroin) with another (eg, cannabis).
10. Treatment programmes routinely assess clients for the presence of infectious diseases (such as HIV/AIDS, hepatitis B and C and tuberculosis) and provide clients with counselling to help them reduce their infection risk (McGovern & Carroll, 2003; NIDA, 1999). Strong associations have been found between substance use and sexual risk behaviours that contribute to the transmission of infectious disease, particularly HIV/AIDS (see Parry & Pithey, 2006, for a review). For instance, substance use is associated with disinhibition and impaired judgment, which may lead to sexual risk behaviours, such as inconsistent condom use. In addition, substance users may engage in unsafe sexual practices in exchange for drugs or money to buy drugs (Rawson et al, 2008; Strathdee & Sherman 2003). Given these associations, access to HIV risk-reduction services within the course of substance abuse treatment is an important quality of care recommendation (Branson et al, 2006; Farrell et al, 2005; Grella et al, 2000). Furthermore, substance abuse treatment facilities are strategic settings for addressing risk behaviours because they offer access to a high-risk population (Birkhead et al, 2007; Lott et al, 2006) and provide opportunities to intervene with people at risk for HIV at a time when they are possibly receptive to such an intervention (Grella et al, 2000). Despite the high prevalence of HIV/AIDS in South Africa, just over 40% of treatment facilities in seven of the nine provinces provide clients with testing and counselling for HIV/AIDS or other infectious diseases (Myers, 2010). This service gap leads to missed opportunities to prevent new infections and reduce HIV and other infectious disease transmission among those

who are already infected. This raises concerns about the quality of services provided to clients at high risk for contracting HIV, and points to the need to improve access to HIV risk-reduction services within South African substance abuse services.

11. It is important to recognise that recovery from substance dependence is a long-term process that may require multiple treatment episodes. As substance dependence is typically a chronic disorder characterised by occasional relapses, once-off treatment often is not sufficient to facilitate sustained behaviour change (Gossop, 2006; NIDA 1999). This is partly due to the fact that long-term drug use results in significant changes in brain functioning that last after the individual ceases drug use (NIDA, 1999). Consequently, many individuals require prolonged or multiple episodes of treatment to achieve sustained abstinence and fully restored functioning. Participation in self-help support and aftercare programmes following treatment often is helpful in maintaining abstinence (Miller, 2009; Moos, 2007).

Pharmacotherapeutic management of substance use disorders

Background and challenges

Over the past few decades, our understanding of the neurobiological basis of substance use disorders has expanded in parallel with rapid advances in the field of neuroscience. Consequently, treatments for substance use disorders have increasingly incorporated pharmacological modalities. Although in many respects still in its infancy, pharmacological treatment modalities can contribute substantially to a multimodal treatment approach within the field of addiction. This is despite the fact that certain pharmacological treatment approaches, such as substitution-based therapies, present conceptual and moral challenges to established practitioners, for whom abstinence-based models may remain the predominant treatment philosophy (Rosenberg & Phillips, 2003), and that pharmacotherapy for addiction is a relatively new field even in medicine (Fleming et al, 1999; Miller et al, 2001). Pharmacological approaches to addiction treatment also face political challenges, such as lack of reimbursement from government and private medical insurance companies. Although the medical model for addictive disorders clearly underlines the nature of addiction as a chronic condition of a relapsing and remitting nature, funding agencies and institutions abroad and locally often do not reimburse pharmacotherapies for addictive disorders, and addictive disorders do not form part of the chronic conditions qualifying for prescribed minimum benefits, according to the South African Board of Health Care Funders. Health economic analyses also indicate substantial financial benefits in improving quality of life and cost effectiveness in the pharmacological treatment of addictive disorders (Connock et al, 2007).

This section reviews the quality of evidence in the pharmacotherapeutic treatment for various substances of abuse. The focus will be on treatments for alcohol, opioid and nicotine use disorders for which approved pharmacological treatments exist. Although drug detoxification mostly takes place in medical and acute emergency settings, the management of detoxification is also discussed, as this may be of interest as background information to the practitioner who will come into contact with patients who require, are currently undergoing or have had detoxification treatments.

Alcohol use disorders: treatment of alcohol withdrawal syndromes

Although the majority of detoxifications for alcohol withdrawal can be conducted on an outpatient basis, up to 25% of patients who discontinue alcohol will develop severe withdrawal syndromes which may require inpatient detoxification (Kraemer et al, 2003). An important part of the clinical assessment is to determine which patients need inpatient detoxification. Risk factors for complicated withdrawal include a past history of complicated withdrawal associated with delirium tremens, or withdrawal seizures, in the context of ongoing severe dependence with a high daily alcohol intake (Schuckit et al, 1995). Other indicators for inpatient treatment include a past history of failed outpatient detoxification, poor social support structures and comorbid medical conditions. Clinical parameters shown to be predictive of delirium tremens in particular include increased systolic blood pressure, tachycardia, high number of past seizures and hyperpyrexia in the context of withdrawal (Monte et al, 2009; Palmstierna, 2001). The prevalence of complicated withdrawal characterised by delirium tremens and/or withdrawal-related seizures varies from 5% to 12% (Mayo-Smith, 1997, Schuckit et al, 1995). The aims of managing severe withdrawal include the prevention and amelioration of distress, discomfort and anxiety associated with withdrawal, the prevention of withdrawal delirium (delirium tremens), including the development of Wernicke's encephalopathy, as well as the prevention of withdrawal-related seizures (see Box 18.2 for summary).

Most treatment guidelines advise treatment with a long-acting oral benzodiazepine, such as diazepam or chlordiazepoxide, administered as a reducing regime (Mayo-Smith, 1997; Mayo-Smith et al, 2004). In the South African setting, the most commonly used drug is diazepam, a drug which binds to the major inhibitory receptors in the brain, the gamma-aminobutyric acid, or $GABA_A$ receptor complex. Binding to the gamma subunit of this receptor facilitates the GABA interaction with other GABA receptor subunits, which in turn increases the frequency of influx of chloride ions across neuronal membranes leading to membrane hyperpolarisation. The starting dose of the drug is determined by a clinical assessment of the severity of the withdrawal syndrome, and rating scales such as the Clinical Institutes of Withdrawal Assessment for Alcohol scale (CIWA-Ar scale) can aid in this process (Sullivan et al, 1989). It is important for clinicians to be flexible and to titrate the dose of benzodiazepines to the patient response in order to avoid under- or overtreatment. Three approaches on the initiation of benzodiazepine withdrawal regimes are described in the literature (Saitz & O'Malley, 1997):

1. The frontloading approach involves starting the patient on high initial doses (20 mg of diazepam) repeated every two hours in order to prevent withdrawal.
2. The fixed-dose regime involves the prescription of 6-hourly benzodiazepines (usually 20 mg of diazepam), with as-needed doses for breakthrough symptoms in between.

Box 18.2: Therapeutic goals of alcohol detoxification

- Amelioration of withdrawal symptoms such as anxiety, autonomic hyperactivity
- Prevention of alcohol withdrawal delirium (delirium tremens)
- Prevention of withdrawal seizures
- Prevention of Wernicke's encephalopathy.

Possible problems with these two regimes include risk of over-sedation and emphasise the need for flexibility on the part of clinicians.

3. The 'symptom trigger' method involves the regular monitoring for withdrawal symptoms and the administration of benzodiazepines when clinical symptoms reach a threshold above 8 on the CIWA-Ar scale. There is some evidence that initiation of pharmacotherapy after the emergence of symptoms (symptoms trigger approach) produces superior (yet non-significant) outcomes in terms of symptom relief (Ntais et al, 2005).

Longer-acting benzodiazepines, such as chlordiazepoxide and diazepam, are preferred as they have lower abuse potential. Diazepam reaches peak plasma levels as rapidly as one to two hours hours after oral ingestion, and is metabolised in the liver to an active metabolite desmethyldiazepam, which has a long half-life of over 40 hours. Since diazepam is highly lipophilic, it is rapidly distributed in brain tissue and has a relatively fast onset of action. Redistribution into muscle and fat tissue also accounts for the dissipation of its effects (Trevor & Way, 1998). In turn, liver abnormalities in alcohol-dependent patients can also lead to accumulation and decreased breakdown, making short-acting medications such as oxazepam and lorazepam, which are not metabolised into active metabolites, more attractive in this population (Trevor & Way, 1998; Mayo-Smith et al, 2004).

There still remains controversy over the role of benzodiazepines versus anticonvulsants and other drugs such as beta-blockers, alpha-adrenergic agonists such as clonidine, and neuroleptics in the amelioration of withdrawal-related symptoms. Whereas benzodiazepines provide no clear statistically significant benefits, as assessed in meta-analyses in the lessening of withdrawal symptoms in comparison to these medications, benzodiazepines are significantly more likely to prevent withdrawal seizures (and delirium) in comparison to placebo. However, in comparison to some anticonvulsants, such as carbamazepine, benzodiazepines appear to be equivalent in the prevention of withdrawal seizures. Data on the efficacy of anticonvulsants in the treatment of other withdrawal related symptoms is, however, limited (Ntais et al, 2005).

Prophylactic treatment of Wernicke's encephalopathy is critical in any patient presenting with features suggesting acute confusion associated with malnutrition or signs of peripheral neuropathy. Wernicke's encephalopathy is characterised by delirium with ophthalmoplegia, ataxia, memory disturbance, hypothermia and hypotension, and has important preventable complications such as persistent amnestic disorder (Korsakoff's psychosis). Current recommendations are the use of parenteral vitamin B_1 (thiamine) in the form of intravenous or intramuscular preparations. Treatment usually consists of one to two ampoules diluted with crystalloids administered three times daily for the first two days and daily thereafter for

Box 18.3: Important considerations in the detoxification of patients with alcohol dependence

- The majority of patients can be detoxified on an outpatient basis.
- Severe alcohol withdrawal is a potentially life-threatening condition with high morbidity and mortality.
- Moderate to severe withdrawal should be managed in a medical setting staffed and equipped to manage this condition and its potential complications.

five days. Co-administration of vitamins B_2 and B_6 should occur concurrently. Intravenous administration must be carefully monitored, as anaphylactic responses have been reported in rare cases. Intravenous glucose should never be administered prior to thiamine as it can result in increased thiamine depletion and precipitate Wernicke's encephalopathy (Thomson et al, 2002).

Alcohol use disorders: maintenance pharmacotherapies in relapse prevention

The principle aim of maintenance pharmacological treatments is to prevent relapse after successful detoxification. Of the maintenance pharmacotherapies available, many target triggers of relapse into drug use that are associated with craving experiences. These medications can therefore be conceptualised as anti-craving agents. Craving can be categorised into positive or Type I craving, which is primarily associated with the appetitive and motivational drives, as well as the desire to re-experience subjective feelings of a rush. Type I craving is postulated to be associated with impulsivity and dopaminergic dysregulation within the nucleus accumbens, driving drug-taking behaviour and positive reinforcement of drug-taking behaviour. Type II craving, or negative craving, is related to negative reinforcement, and associated with compulsive behaviours and increased drug-seeking behaviour, with the primary aim of ameliorating the negative affective state that characterises protracted withdrawal syndromes (Koob & Le, 2008; Koob, 2009). Other mechanisms of pharmacological maintenance medications, such as disulfiram, include the induction of aversive states (sensitisation) when alcohol is consumed, leading to decreased use of alcohol.

One postulated mechanism whereby alcohol produces its reinforcing effects is via the increased release of endogenous opioids. Endogenous opioid secretion increases the release of dopamine directly via stimulation of the nucleus accumbens, or indirectly by inhibiting the tonically inhibitory effect of GABA neurons on dopamine neurons within the nucleus accumbens (Gianoulakis, 2009). Evidence from randomised controlled trials and meta-analyses have supported the use of naltrexone, an opiate antagonist, in the maintenance treatment of alcohol dependence. As an antagonist of mu-opiate receptors, naltrexone blocks the stimulation of beta endorphins on opiate receptors, which in turn is postulated to result in less dopamine release in the nucleus accumbens. In a meta-analysis of 27 randomised controlled trials, comprising over 4 000 patients, naltrexone has been shown to significantly reduce relapse into heavy drinking for 36% of patients (number needed to treat [NNT] = 7). In addition, time to any alcohol use was also reduced for 13% of patients (NNT = 12) (Srisurapanont & Jarusuraisin, 2005). The results from the largest multicentre randomised controlled trial, the COMBINE study, support the findings of

Box 18.4: Craving and associated mechanisms of learning

- Type I craving: associated with dopaminergic drive, increased seeking of 'high' experienced during intoxication. Drug-taking behaviour positively reinforced.
- Type II craving: Negative affective states, protracted withdrawal. Negative reinforcement. Increased drug-taking to avoid unpleasant states.

meta-analyses that demonstrate a significant reduction in heavy drinking days over the short term, as well as the return of drinking after a one-year follow-up. Of note is a significant interaction effect seen in this study for combined naltrexone and cognitive behavioural therapy, emphasising the importance of combined psycho-social and pharmacological approaches (Anton et al, 2006). It should be noted, however, that most studies were only 12 weeks in duration, and despite no additional benefit in the short term of enhanced psycho-social treatment, in combination with naltrexone over placebo treatment, psycho-social treatment played a critical mediating role in the medium term on the impact of naltrexone on alcohol use. Whereas the daily dose was 50 mg in the majority of studies, the COMBINE study used a 100 mg dose. Naltrexone is well tolerated in the majority of patients. Contraindications include abnormalities in liver function and the comorbid presence of opioid dependence. Monitoring requirements include baseline and follow-up liver enzymes. The concurrent use of medications that are potentially hepatotoxic (such as disulfiram) as well as opioids containing analgesics should be avoided. At the time of writing, naltrexone is not registered in South Africa but can be acquired following application and approval on named-patient basis to the Medicines Control Council (MCC) of South Africa.

A large body of evidence exists for the efficacy of acamprosate, an agent which attenuates hyperglutamergic states via its action on glutamate N-Methyl-D-Aspartate (NMDA) receptors, in the maintenance treatment of alcohol dependence. Glutamate is the major excitatory neurotransmitter in the human brain, and both acute as well as protracted alcohol withdrawal are characterised by increased glutamate and NMDA receptor activity, with resulting negative affective states characteristic of Type II craving. Acamprosate, or calcium acetylhomotaurinate, has a similar structure to the amino acid taurine, and via its action on metabotropic NMDA receptors is thought to attenuate the hyperglutamatergic state that characterises protracted alcohol withdrawal (Scott et al, 2005). In a meta-analysis of 17 randomised controlled trials, acamprosate was significantly superior to the placebo in increasing the time of continuous abstinence from alcohol at six-months follow-up after detoxification. NNT at 6 months was 7.8, indicating that this medication is equivalent, and even superior, to treatments routinely used in prevention of adverse events in other medical conditions, such as ischaemic heart disease and hyperlipidaemia (Mann et al, 2004). Despite evidence of its efficacy in European studies, the COMBINE study, including another US study, failed to show the superiority of acamprosate over the placebo (Anton et al, 2006). It has been suggested that methodological issues, including differences in sample characteristics between the US and European studies, such as the degree of associated psycho-social rehabilitation treatments received, account for the lack of separation from the placebo in these studies. Subgroup analyses also revealed that patients who were more motivated to remain abstinent fared better with acamprosate. In a further meta-analysis, it was shown that acamprosate has a greater effect at preventing lapses (time to first drink) and had little effect once drinking restarted. In contrast, naltrexone had greater effect at preventing lapses turning into a full-blown relapse (Rosner et al, 2008). Despite these findings, acamprosate did not confer any additional benefit in combination with naltrexone, even when administered with a concomitant behavioural intervention, in comparison to naltrexone alone (Anton et al, 2006).

Other candidate drugs in the maintenance treatment of alcohol dependence include topiramate, a drug which is thought to both enhance $GABA_A$ inhibitory activity over the positive reinforcing effects of dopamine in the nucleus accumbens (Type I craving) and attenuate glutamatergic hyperactivity via its action on AMPA glutamatergic receptors (Type II craving). In turn, it is thought that the decrease of glutamatergic activity results in decreased dopamine release in the nucleus accumbens (Kenna et al, 2009). Two randomised controlled trials, one a multisite trial, have demonstrated the superior efficacy of topiramate over the placebo on a number of outcome measures, such as the time abstinent from drinking, the level of self-reported drinking, compulsive cravings for alcohol and improved physical and psycho-social wellbeing (Johnson et al, 2003; Johnson et al, 2007; Johnson et al, 2008).

Disulfiram, which has been in use since the 1970s, is classified as an alcohol sensitising agent and acts as an inhibitor of acetaldehyde dehydrogenase which leads to an accumulation of acetaldehyde, causing an unpleasant reaction characterised by flushing, hypotension, nausea, vomiting and headaches upon use of alcohol. In addition, its inhibition of dopamine beta hydroxylase may also contribute to its mechanism of action by altering dopaminergic regulation. Disulfiram has been demonstrated in a large multisite RCT in the United States conducted in the 1980s to be no more effective than the placebo in preventing relapse into alcohol use (Fuller et al, 1986). However, the high dropout rate in this study (80%) could accounted for the lack of a positive finding. Despite its lack of separation from placebo, more recent randomised controlled trials that included supervised forms of treatment, such as the inclusion of supportive family members in treatment monitoring with disulfiram, have demonstrated a clear benefit in these studies (De Sousa et al, 2008a; Laaksonen et al, 2008). Despite the likelihood of bias due to non-blinding in these studies, disulfiram was superior to acamprosate, naltrexone and topiramate on a number of measures, which include increased time to relapse and longer times of abstinence, including lower levels of abnormal liver function tests. Patients treated with topiramate, naltrexone and acamprosate, however, showed less craving than those treated with disulfiram (De Sousa et al, 2008b; De Sousa & De Sousa, 2004; De Sousa & De Sousa, 2005; Laaksonen et al, 2008).

In recent years, baclofen, a $GABA_B$ receptor agonist, has received increasing attention in pharmacotherapy trials for alcohol maintenance (Addolorato et al, 2009). The fact that it is not metabolised in the liver makes it an attractive alternative for patients with alcohol dependence and existing liver damage (Garbutt & Flannery, 2007). Three randomised controlled trials have been conducted to date, with two showing significant superiority over the placebo in reducing alcohol intake and prolonging periods of abstinence from alcohol (Addolorato et al, 2002; Addolorato et al, 2007; Garbutt et al, 2007). A third trial conducted in the US failed to replicate these findings, and further research is necessary to clarify the role of baclofen in the treatment of alcohol dependence (Garbutt et al, 2007).

Because of their relative low cost in the developing world, medications such as disulfiram and baclofen are of particular relevance to middle-income countries such as South Africa (Thirthalli & Chand, 2009). As the side-effect profile of disulfiram may be problematic, requiring specialist monitoring, and as the evidence base for these agents is still comparatively small, pragmatic trials utilising these agents are of interest in the local context (Benegal et al, 2009).

Table 18.2: Maintenance pharmacotherapy for alcohol dependence

MEDICATION	LEVEL OF EVIDENCE
Naltrexone	Cochrane review and meta-analysis of 27 RCTs.[1] Small to medium effect size, NNT = 7 for prevention of relapse in short-term treatment, NNT = 13 for increase in time to next drink.
Acamprosate	Meta-analyses of 17 RCTs.[2] Small to medium effect sizes. NNT = 7.5 at 12 months for abstinence.
Disulfiram	Three different RCTs.[3] One negative trial. Positive trials show that supervised consumption results in superior outcomes for disulfiram compared to other agents.
Baclofen	Three RCTs.[4] Two positive. One negative trial.
Topiramate	Two positive RCTs.[5] One multisite study.

Notes
[1] Srisurapanont & Jarusuraisin, 2005
[2] Mann et al, 2004; Bouza et al, 2004; Kranzler & Van, 2001
[3] De Sousa et al, 2008b; Fuller et al, 1986; Laaksonen et al, 2008
[4] Addolorato et al, 2002; Addolorato et al, 2007; Garbutt et al, 2007
[5] Johnson et al, 2003; Johnson et al, 2008

Opioids: detoxification

The cessation of opioid use in individuals dependent on opioids is characterised by a highly unpleasant withdrawal syndrome, consisting of anxiety, dysphoria, restlessness, craving, irritability, increased sweating, pupillary dilation, lacrimation, rhinorrhoea, muscle cramps, abdominal cramps, nausea, vomiting, diarrhoea, raised blood pressure and increased heart rate (American Psychiatric Association, 2005). Whereas less severe withdrawal syndromes can occur with opioids other than heroin, the following discussion will focus on the detoxification of heroin.

In contrast to alcohol withdrawal, which represents a condition with considerable morbidity and mortality, opioid withdrawal is rarely ever dangerous. The acute syndrome reaches a peak 48–72 hours after the last dose of opioids and resolves within 7–10 days (Mattick & Hall, 1996). Following this acute phase, users often report a more protracted cluster of symptoms, which can be conceptualised as protracted withdrawal associated with Type II craving. This is characterised by symptoms of malaise, craving of opioids, lack of a sense of pleasure, fatigue and negative mood states (Shi et al, 2007).

Medications used in the detoxification of heroin include medications that act as substitution drugs, such as buprenorphine or methadone, both of which act as agonists to stimulate the mu-opioid receptor. Whereas methadone is a full agonist at mu-opioid receptors, buprenorphine acts as a partial agonist with high receptor affinity but low intrinsic activity. These qualities of buprenorphine result in less pronounced opioid effects at higher doses, and a consequent ceiling effect. As a result, this medication is safer in overdose, and users report less somnolence and sedation with its use (Walsh & Eissenberg, 2003). In contrast to methadone, which can lead to QT_c prolongation and subsequent cardiac dysrythmias, buprenorphine is likely to result in significantly less QT_c interval prolongation (Wedam

et al, 2007). Because of its partial agonist properties, it is important that buprenorphine be initiated only once a patient has shown signs of early withdrawal, as it can precipitate withdrawal by replacing heroin from mu-opioid receptors. Other medications used in the detoxification of heroin include clonidine, an alpha-receptor agonist which acts to attenuate adrenergic hyperactivity associated with opioid withdrawal. Although clonidine ameliorates withdrawal-associated symptoms at equivalent rates to methadone and results in faster completion of withdrawal, it has little effect on the intense cravings and dysphoria associated with opioid withdrawal, and causes significantly more adverse effects and treatment drop-outs due to side effects such as hypotensive episodes (Gowing et al, 2009b).

In the South African context, three different preparations are available for opioid substitution and detoxification treatments. These are buprenorphine (Subitex), Suboxone (buprenorphine:naloxone in a 4:1 combination) and high-concentration 2 mg/ml methadone. Suboxone contains the opoid agonist buprenorphine, in addition to the opioid antagonist naloxone. The latter is added to discourage intravenous or intranasal use of buprenorpine (see section on diversion of agonist treatments). Although available in the private sector, these medications are currently not available in the public sector, apart from limited use by state-funded inpatient detoxification treatment facilities. The current cost of these medications, including concentrated methadone, limits their use even in the private sector to those who can afford substantial monthly payments.

The aim of detoxification should always be to prepare a patient for intensive psycho-social rehabilitation, as detoxification on its own serves little purpose and is a poor use of resources (Darke et al, 2007; Weich et al, 2008). As many as 72% of patients fail detoxification on placebo, a rate similar to the successful self-detoxification with no pharmacological assistance reported by opioid-dependent persons (Gossop, Battersby & Strang, 1991; San et al, 1992). Systematic reviews have demonstrated that opioid-agonist treatment in the form of methadone is significantly more effective than the placebo in controlling symptoms of opioid withdrawal, and leads to higher completion rates of withdrawal than placebo. However, in meta-analyses methadone appears equally efficacious in attenuating withdrawal symptoms, in comparison with other pharmacological agents, such as buprenorphine, clonidine and chlordiazepoxide (Amato et al, 2005)

In the context of randomised controlled trials, inpatient detoxification with methadone results in drug-free completion of detoxification in up to 70–80% of patients, whereas outpatient detoxification is successful in only 17–34% of patients (Gossop et al, 1986; Wilson et al, 1975). Despite these findings, and the wide availability since the Second World War of medications such methadone and clonidine, the current quality of evidence regarding the indications for in- versus outpatient opiate detoxification is surprisingly poor. This is particularly problematic for developing countries such as South Africa, given the likely higher cost of inpatient detoxification. This is further compounded by the availability of medications such as buprenorphine and the buprenorphine-naloxone combination that allow for the possibility of office-based opioid substitution prescribing and community-based outpatient detoxification (Parran et al, 2010; Sullivan & Fiellin, 2008). In one RCT comparing buprenorphine to methadone, however, the completion rate of outpatient detoxification was as high as 77% for the buphrenorphine group, with a tendency, although non-significant, for buprenorphine patients to stay in treatment longer and complete withdrawal more often

(Bickel et al, 1988). A Cochrane review conducted to determine the effectiveness of in- versus outpatient detoxification concluded that current evidence is insufficient to conclude whether inpatient detoxification is more effective than outpatient detoxification, and that more research is needed (Day, Ison & Strang, 2005; San et al, 1992).

The quality of the existing research in this field also suffers from serious methodological deficiencies, such as small sample size, inadequate randomisation procedures and failure to conduct intention-to-treat analyses, therefore possibly overestimating the beneficial effects of inpatient detoxification. In addition, all the studies examining the differences between in- and outpatient approaches used methadone as detoxification medication (Day et al, 2005). In turn, systematic reviews have shown that psycho-social treatments on an outpatient basis can enhance treatment retention and decrease opiate use, as well as increase compliance with follow-up visits when administered concurrently with buprenorphine or methadone down-taper regimes (Amato et al, 2008a). In comparison to clonidine and lofexidine, buphrenorphine is significantly more effective in treating withdrawal symptoms, resulting in significantly higher rates of detoxification completion and lower rates of treatment drop-out due to adverse effects. In addition, there is some evidence that resolution of withdrawal symptoms is quicker with buphrenorphine, in comparison to methadone, and completion of detoxification more frequent, although this finding did not reach statistical significance in meta-analyses (Gowing et al, 2009a).

In the clinical setting, factors that impact on the decision to detoxify patients in an inpatient versus outpatient setting will include the level of severity of the dependence, associated social circumstances as well as psychiatric or physical comorbidity. Clinically significant withdrawal typically develops only after two weeks of daily opioid use. Opioids with a short half-life, like heroin, are also more likely to result in more pronounced withdrawal syndromes. Patients who use opioids intermittently, and not on a daily basis, are also likely to experience less pronounced withdrawal syndromes. As the social support structure of many opioid-dependent patients is likely to be poor, with homelessness and a chaotic lifestyle not uncommon, many patients with more severe dependence syndromes, which may also present with comorbid psychiatric, polydrug and medical problems, are likely to be suitable only for inpatient detoxification (Silins et al, 2008). As detoxification, with the aim of referral to follow up abstinence-oriented psycho-social rehabilitation programmes, is likely to play an important role in stepped-treatment approaches in the developing world, detoxification strategies for opioid withdrawal are likely to continue to be relevant treatment approaches within the South African context. The low availability of detoxification services across geographic areas in South Africa makes inpatient detoxification a more attractive option for patients who live far from available services. More research is needed, however, to clarify which patients will do better with inpatient detoxification and what benefits inpatient detoxification may have over and above outpatient approaches. Economic cost analyses of inpatient detoxification versus outpatient detoxification with psycho-social augmentation are also required.

Opioids: maintenance pharmacotherapies

Long-term prospective research has demonstrated that abstinence-based community residential rehabilitation programmes of adequate duration can be successful for opioid-

dependent patients, with up to 50% achieving abstinence at a five-year follow-up (Gossop et al, 2003). Nevertheless, a subgroup of patients with severe heroin dependence is unlikely to succeed with traditional abstinence-based approaches and may require harm-reduction approaches that consist of opioid substitution-maintenance prescribing. The aims of substitution-maintenance treatment are several, and include:

- The reduction of illicit heroin use
- the reduction of associated health risk behaviours such as needle-sharing and risky sexual practices to procure drugs and number of injections
- preventing transition to injection use among non-injection users
- reducing associated criminal activity and mortality associated with overdoses.

During substitution-maintenance treatment patients are given the opportunity to reconstruct their lives and improve their psycho-social and occupational functioning in order to obtain greater stability. Maintenance treatments can be time-limited over 12 to 24 months but may be a treatment option over many years.

The World Health Organization (WHO) has published a position statement and guidelines on the treatment of persons with opioid dependence across countries. It is recommended that substitution-maintenance programmes be made available in developing countries depending on financial feasibility (WHO, 2009). The UNODC (United Nations Office on Drugs and Crime) and its Commission on Narcotic Drugs have also published position statements highlighting the vital role that substitution treatments play in the prevention of transition to intravenous use among non-injection opiate users and also the prevention of HIV infection among opiate users who inject their drugs. Evidence from the literature supports the use of methadone and buprenorphine as the mainstay substitution medications in the treatment of heroin dependence. Meta-analyses from systematic Cochrane reviews have demonstrated that methadone and buprenorphine are successful in significantly reducing illicit opioid use, associated risk behaviours and transition to injection drug use, and result in greater treatment retention of patients (Mattick et al, 2008; Mattick et al, 2009). Although criminal activity and mortality was not significantly reduced in a meta-analysis of randomised control trials (Mattick et al, 2009), evidence from some prospective cohort studies supports a reduction in criminal activity and mortality found in controlled treatment trials (Gossop et al, 2003). Buprenorphine has also been demonstrated to be significantly superior to a placebo as an effective maintenance treatment, although it is somewhat less efficacious than methadone, particularly high-dose methadone maintenance treatment (Mattick et al, 2008). Despite the evidence in favour of methadone's superiority in substitution treatment, including its lower cost, and side-effect profiles that include higher levels of sedation and somnolence, the availability of buprenorphine as an alternative is recommended by the WHO (WHO, 2009).

For substitution-maintenance prescribing to be effective, it is critical to ensure that certain minimum standards are adhered to. These include the provision of fully equipped facilities and trained staff to manage patients on substitution treatments. This includes facilities for spot urine testing, the availability of resuscitation equipment and staff trained in supervised consumption of maintenance treatments (Weich et al, 2008; WHO, 2009). Although these requirements are often perceived as barriers to participation in delivering

substitution therapies (Barry et al, 2009), the lack of supervised consumption is likely to lead to diversion of treatments in order to fund the procurement of illicit heroin and the practice of injecting medications such as buprenorphine to obtain a high (Winstock et al, 2009). In this regard, treatments such as the naloxone–buprenorhine combination (Suboxone) are likely to be useful in cases where injection or diversion of burprenorphine is problematic. Although abuse potential is much less likely with Suboxone, it is still possible (Mammen & Bell, 2009). This medication is taken sublingually in its therapeutic form, which leads to inadequate absorption of naloxone, an opioid receptor antagonist or blocker, with no incipient unpleasant withdrawal reaction. Upon intravenous administration, naloxone is activated due to higher bioavailability, leading to the precipitation of unpleasant withdrawal. Given adequate mechanisms of maintaining patient confidentiality, a national register of patients on agonist maintenance treatment should be considered in order to prevent doctor-shopping and double prescription that can, in turn, fuel diversion practices (Weich et al, 2008).

Systematic reviews have demonstrated that additional psycho-social interventions in the detoxification phase can provide significant benefits in retaining more participants in treatment for longer (Amato et al, 2008a). However, the addition of specific psychotherapeutic interventions, such as contingency management, cognitive behavioural therapy, psycho-analytical psychotherapy and various forms of counselling, as well as routine psycho-social interventions, in methadone maintenance treatments have been shown in a Cochrane meta-analysis to provide no additional benefits in terms of retention in treatment, opiate use, treatment compliance or improvement of psychiatric symptoms or depression (Amato et al, 2008b). Higher abstinence rates did, however, occur in a subsample of patients within this meta-analysis.

Despite evidence of the efficacy of maintenance therapies with opioid agonists, compared to placebo or wait-list controls, important unanswered questions exist about the effectiveness of opioid agonist therapies in comparison to other abstinence-based and residential psycho-social therapeutic approaches. Naturalistic cohort studies have shown comparable long-term abstinence and heroin-use rates between longer-term residential psycho-social interventions and methadone maintenance treatments (Darke et al, 2005; Gossop et al, 2003; Hubbard et al, 2003). However, cohort studies suffer from methodological shortcomings, such as attrition bias, and are not designed to determine efficacy. This underscores the importance of pragmatic randomised controlled trials directly comparing agonist maintenance treatments with active psychological treatments and residential rehabilitation of adequate duration. The option and availability of methadone maintenance as the treatment choice in the developed world may complicate the design and feasibility of such research. This may not be the case in populations from the developing world, in which the effectiveness of maintenance treatments have not been established. In addition, cost analysis studies are needed to analyse the likely economic feasibility of maintenance treatments in the South African context.

There are many structural, political and financial factors that pose significant challenges to maintenance-substitution prescribing within the developing world context. Despite these challenges, given the likely increases in heroin use in the future, policy-makers will have to draft and implement clear and specific guidelines as to the suitability of these treatments within a low- to middle-income country such as South Africa. In light of the likely future

increases in intravenous use of heroin, with the consequent risk of HIV infection, harm-reduction approaches such as needle exchange programmes and substitution-maintenance prescribing are becoming even more relevant treatment modalities (Carrieri et al, 2006). In turn, evidence suggests that agonist maintenance programmes can reduce needle-sharing and the prevalence of injection practices that fuel the transmission of blood-borne viruses such as HIV and hepatitis B and C, although few randomised controlled trials have been conducted to estimate efficacy (Gowing et al, 2008). One role for substitution-maintenance programmes would be in a stepped-care package, where opioid substitution maintenance is indicated for patients who have failed to achieve abstinence or a significant reduction of illicit heroin and drug use following treatment in at least one abstinence-based residential rehabilitation programme of reputable quality, and where the treatment was of sufficient duration and adequate aftercare was received. Guidelines are available for maintenance treatments in the South African context (see Weich et al, 2008, for practical treatment guidelines). There exist several important requirements for practitioners and institutions who want to practise opioid-substitution prescribing, and many of these requirements require the urgent adoption and publication of a nationwide policy framework and position statement on the relevance and use of opioid-substitution prescribing within the South African context. Although some of these policy frameworks are receiving attention in the National Drug Master Plan and Prevention of and Treatment for Substance Abuse Bill, the Department of Health will need to address the question of substitution maintenance with attention to particulars and details, and ensure medical practitioners are adequately trained in appropriate prescribing protocols. Table 18.3 highlights some of the important unaddressed problems that need attention. The importance of research programmes are paramount in these initiatives, as their effectiveness and differential effectiveness above and beyond various alternative treatments need to be established within the South African health system.

Table 18.3: Areas in need of attention in the development of substitution-maintenance prescribing in South Africa

- Adoption of national government policy on the use of substitution prescription for opioid dependence. Adoption of particulars with regards to substitution prescribing in the Prevention of and Treatment for Substance Abuse Bill.
- A committee of experts needs to be established under the leadership of the Department of Health in order to develop guidelines and policies on opioid-substitution prescribing.
- Provincial and national funding provision for research to investigate the effectiveness of substitution prescribing with and without concomitant psycho-social approaches within the South African context.
- Development of educational platforms within universities and teaching hospitals to train and certify practitioners as competent in substitution prescribing.
- Mechanisms of accreditation through the HPCSA and Colleges of Medicine for institutions, private practices and practitioners in the prescription of substitution medications for detoxification and maintenance.
- Engagement with Departments of Health and Social Development, as well the private medical insurance sector, to develop remuneration packages for substitution prescribing.

Pharmacotherapy for nicotine, stimulants and cannabis

Nicotine use is highly prevalent in South Africa, with over 26% of the adult and 24% of the youth population smoking tobacco (WHO, 2009). Smoking is a leading cause for mortality and morbidity, and has important health consequences, which range from heart disease to cancer. In the South African context, high rates of HIV and its associated pulmonary complications, such as tuberculosis and lower respiratory tract infections, highlight the importance of treatment of nicotine dependence. Smoking can contribute to higher rates of lower respiratory tract infections and tuberculosis and adversely affect treatment with anti-retroviral medications (Miguez-Burbano et al, 2003; Miguez-Burbano et al, 2005). Over 132 RCTs have been conducted with nicotine replacement therapy (NRT) in assisting smokers who quit in the attenuation of uncomfortable withdrawal symptoms. NRT has been shown in a Cochrane meta-analysis to increase the chance of successfully quitting from 50% to 70% (Stead et al, 2008).

Two medications, bupropion and varenicline, have been approved in the United States for the treatment of nicotine dependence. Of these, bupropion has been approved in South Africa for the treatment of nicotine dependence. Bupropion is thought to act as a noradrenergic and dopaminergic reuptake inhibitor, and results from a Cochrane review have given support for its efficacy in the treatment for nicotine dependence based on the meta-analytic results of over 49 RCTs (Hughes et al, 2007). The tricyclic antidepressant nortriptiline, acting mainly as a noradrenergic reuptake inhibitor, has been demonstrated to have equivalent efficacy to burpropion, although based on the meta-analytic data from only six RCTs. The side-effect profile of nortriptiline has, however, limited its use to that of a second-line off-label agent in the treatment of nicotine dependence. These side effects include high toxicity in overdose, as well as other side effects such as orthostatic hypotension and anticholinergic side effects such as blurred vision, dry mouth and urinary retention. Buproprion is usually prescribed for three months in combination with counselling intervention. The sustained release or extended release formulations can be initiated at 150 mg daily and increased after one week to 300 mg daily. Currently there is no research to suggest that treatment with antidepressants such as bupropion or nortriptiline is either superior or inferior to treatment with nicotine replacement therapy (Hughes et al, 2007). Although not available in South Africa, varenicline, a partial agonist on nicotinic cholinergic receptors, has been shown in a meta-analysis of seven RCTs to increase the chances of successfully remaining abstinent up to two to three times times compared to the placebo (Cahill et al, 2008). In addition, varenicline has been shown to be superior to bupropion and NRT in improving abstinence. Side effects such as agitation and possible depressive ideation or suicidality have led the Food and Drug Administration (FDA) to place a boxed warning on varenicline and bupropion. Further research is needed to determine the relationship between reported suicidality and medications such as varenicline, as reasons for this association remain unclear.

In contrast to the large evidence base of efficacious pharmacological treatments for opioid, alcohol and nicotine addiction, there are no approved treatments with an acceptable level of evidence for the treatment of stimulant or cannabis dependence (Jupp & Lawrence, 2010). Evidence from systematic reviews indicates that the selective serotonin antidepressant fluoxetine shows some benefit in decreasing craving for amphetamines in the short term, but has no effect on relapse rates, or time to relapse. In turn, imipramine at dosages of 150 mg

daily may increase time spent in treatment but has no impact on amphetamine use (Srisurapanont et al, 2001). Treatments that act as agonists and dopaminergic neurons and are therefore based on substitution principles have been used in the treatment of patients with amphetamine and methamphetamine dependence. Dexamphetamine, methylphenidate and bupropion have shown promise over placebo in small, experimental, controlled trials (Elkashef et al, 2008a; Elkashef et al, 2008b; Tiihonen et al, 2007). Findings from these studies await replication. In turn, meta-analyses of pharmacological treatments for cocaine dependence have not shown any clear benefits for dopamine agonists or anticonvulsants and only non-significant and trend-level benefits from single controlled trials for desipramine, an antidepressant, and disulfiram (Amato et al, 2007; Minozzi et al, 2008; Pani et al, 2010; Silva et al, 2010; Soares et al, 2010).

Evidence-based psycho-social models of treatment

Four psycho-social treatment approaches – relapse prevention, motivational enhancement therapy, the Matrix model of treatment and 12-step facilitation – are among the most promising models of treatment and have been shown to be effective for all classes of substances and across a range of contexts, countries (developing and developed) and population groups (adolescents and adults). They are currently being used in South Africa either as stand-alone programmes or to supplement and enhance pre-existing treatment programmes (Fakier & Myers 2008; Myers & Fakier 2007).

Motivational enhancement therapy (MET)

MET is a structured therapeutic approach based on the therapeutic style and techniques of motivational interviewing (Miller & Rollnick, 2002). Initially developed for the treatment of problem drinking, it has since been applied to the treatment of other drug dependencies (Gossop, 2006). It can be used as a stand-alone treatment or as a supplement to pre-existing treatment programmes and is suitable for use in both inpatient and outpatient settings (NIDA 1999; UNODC/WHO 2008). In South Africa, MET has been primarily used as a supplement to pre-existing treatment programmes, although there are several programmes where MET is the primary treatment approach provided.

The primary goal of MET is to evoke rapid and internally motivated behaviour change. To achieve this, MET adopts a client-centred counselling approach which focuses on helping clients resolve their ambivalence about engaging in treatment and changing their substance use. The collaborative therapist-client relationship is seen as a facilitator of behaviour change. Specifically, the therapist fosters a positive, encouraging relationship with the client and uses this relationship to reinforce behaviour change. Therapist-client interactions are direct but never confrontational and focus on building clients' self-esteem and self-efficacy (Apodaca & Longabaugh, 2009; Miller, 1996; Miller & Rollnick, 2002).

The core components of MET include a comprehensive assessment, followed by two to four individual treatment sessions. The comprehensive assessment includes a thorough medical and psychological assessment. The first treatment session focuses on providing feedback generated from the initial assessment. This feedback is designed to stimulate discussion regarding personal substance use, to identify the advantages and disadvantages of

changing current substance use, and to increase readiness to change substance use behaviours through the client identifying a need for change and by the therapist eliciting motivational statements from the client about his/her ability to change (Apodaca & Longabaugh, 2009; Gossop, 2006; Miller, 1996). Motivational interviewing principles are used to strengthen motivation and build a plan for change. As part of developing an action plan, the therapist suggests and discusses coping strategies for high-risk situations. In subsequent sessions, the therapist monitors the client's attempts to change, reviews the degree to which change strategies have been effective (suggesting new strategies where needed), and encourages continued commitment to change (Miller, 1996).

The effectiveness of MET has been widely researched over the past two decades. Findings from multi-site randomised controlled trials demonstrate that participants treated with MET were more likely to be retained in treatment (Ball et al, 2009; Carroll et al, 2009), had greater commitment to treatment goals and better treatment compliance, and had fewer drug-related problems and relapses (Dennis et al, 2004; Miller Yahne & Tonigan, 2003; Stein et al, 2006) than participants assigned to control groups. Similarly, a systematic review of randomised controlled trials of treatments for persons with co-occurring substance dependence and other mental disorders found that persons assigned to MET treatment were more likely to remain in treatment, complete treatment and have fewer post-treatment psychiatric problems than those assigned to a treatment-as-usual control group (Cleary et al, 2009).

Relapse prevention

Relapse prevention (RP) is a cognitive-behavioural therapy initially developed for the treatment of problematic alcohol use by Marlatt and Gordon (1985) and later adapted for other drug use. It can be used as a stand-alone treatment or as part of a more comprehensive treatment programme and is suitable for both inpatient and outpatient settings (Rawson et al, 1993). The model assumes that learning processes play a critical role in the development and maintenance of maladaptive patterns of behaviour, such as substance use. Relapse prevention thus uses a combination of behavioural skills training, cognitive interventions and lifestyle change procedures to equip individuals to achieve and maintain abstinence by avoiding relapse to substance use (Witkiewitz & Marlatt, 2004; Witkiewitz & Marlatt, 2007).

The primary goal of this approach is to teach individuals how to identify, anticipate and cope with situational (external) and emotional (internal) triggers that place them at risk for relapse (Witkiewitz & Marlatt, 2007). Specifically, individuals are taught to identify cognitions, negative moods and external events that trigger thoughts, urges and cravings for alcohol and other drugs (Gossop et al, 2002; Witkiewitz & Marlatt, 2007). Individuals are also taught ways to avoid these triggers and, where this is not possible, cognitive strategies to enhance self-control and cope effectively with high-risk situations. Specific techniques include exploring the positive and negative consequences of continued use, self-monitoring to recognise drug cravings and to identify high-risk situations for use, and strategies for coping with and avoiding high-risk situations and the desire to use (Douaihy et al, 2007; Witkiewitz & Marlatt, 2004; Witkiewitz & Marlatt, 2007).

There is a large body of evidence supporting the effectiveness of RP. For example, a review of controlled clinical trials of RP concluded that, for a range of different substances

of abuse, individuals assigned to RP conditions had better outcomes than those assigned to no-treatment control conditions. Relapse prevention also was found to be as effective as, but not superior to, 12-step facilitation and MET approaches (Carroll, 1996). Other clinical trials found that RP is valuable for reducing the intensity and duration of relapse episodes, if they occur (Gossop, 2006). Also, studies comparing RP to standard counselling approaches found sustained main effects or delayed emergence of effects for relapse prevention (Carroll et al, 1998; Gossop, 2006). In other words, individuals receiving RP treatment show sustained or continued improvement in their coping skills and treatment outcomes compared to individuals who do not receive RP treatment (Carroll, 1996; Carroll et al, 1998; Gossop, 2006). Finally, RP has been found to be equally effective in group and individual formats (Schmitz et al, 1997).

The Matrix model

The Matrix model is an eclectic model that combines elements of several evidence-based treatment approaches (namely, MET, RP and 12-step facilitation) into a single framework. Initially developed for the treatment of stimulant dependence, it has since been shown to be an effective psycho-social treatment for a broad range of substances. While it was originally designed for use as an intensive outpatient model, it has been successfully adapted for use in inpatient settings. The original adult version of the programmes has also been adapted for use with adolescents and various special population groups, including individuals with co-occurring disorders and criminal justice populations (NIDA, 1999; UNODC/WHO, 2008). It is a highly structured programme, with detailed therapist manuals that contain work sheets for each session of the 16-week programme.

Borrowing heavily from RP and MET approaches, this model uses a combination of behavioural skills training, cognitive interventions, lifestyle changes and a motivational interviewing therapeutic style to achieve its objectives. The primary goals of this model are to:

- Engage and retain individuals in treatment for the duration of the 16-week programme
- Facilitate early abstinence from substance use (termed 'early recovery')
- Prevent relapse through providing clients with skills needed to identify, anticipate and cope with stressors and situations that may lead to relapse (Huber et al, 1997; Rawson et al; 1995). In this model, client engagement and retention in treatment (and positive behaviour change) are facilitated through the therapist–client relationship. The therapeutic style borrows heavily from motivational interviewing, whereby the interaction between the therapist and client is realistic and direct but not confrontational. In addition, therapists are trained to conduct treatment sessions in a way that promotes the client's self-esteem, self-efficacy to change, dignity and self-worth (Rawson et al, 1995).

Apart from this therapeutic style, other core components include the following:

- Psycho-education, during which patients and their families learn about issues critical to addiction and relapse (especially the effect of substances on brain neurochemistry and functioning, the development of and recovery from substance dependence, and how to identify triggers and high risk situations)

- Structured, manualised group counselling sessions comprising early recovery groups, during which strategies to achieve early recovery are discussed, and relapse prevention groups, during which skills critical to maintaining abstinence are developed
- Individual sessions, where clients receive direction and support from a trained therapist
- Exposure to and participation in twelve-step self-help programmes
- Participation in social support groups, during which clients develop abstinence-oriented social networks.

Much of the focus of this approach is on group work. The programme also includes family education and conjoint/family counselling sessions for family members and significant others affected by substance use. In addition, all individuals are monitored for substance use through breath and urine testing (Obert et al, 2002; Rawson et al, 1995).

Several evaluations of the Matrix model have been conducted over the past 15 years. Findings from these evaluations demonstrate that participants treated with the Matrix model show statistically significant reductions in substance use, improvements in psychological indicators, and reductions in sexual risk behaviours associated with HIV transmission (Huber et al, 1997; Obert et al, 2005; Rawson et al, 2002). The most compelling evidence for the effectiveness of the Matrix model comes from the Methamphetamine Treatment Project. This project compared the Matrix model of treatment with treatment-as-usual (TAU) at eight different sites. Across sites, significantly better treatment retention and completion rates were found for individuals assigned to the Matrix model, compared to the TAU group. Significantly greater reductions in drug use, better abstinence rates and longer periods of abstinence were found for individuals assigned to the Matrix model, compared to individuals assigned to the TAU condition (Galloway et al, 2000; Huber et al, 2000; Obert et al, 2005; Rawson et al, 2002).

In South Africa, the Matrix model has been successfully adopted by outpatient, day-patient and inpatient treatment services in the Western Cape. It is also being introduced into several other provinces, including Free State and Gauteng. The programme materials are being translated into local languages, and an impact evaluation of one local programme is in the process of being conducted.

Twelve-step facilitation therapy (TSF)

Twelve-step facilitation (TSF) therapy is a structured, manual-driven approach to enabling early recovery from substance dependence. It is implemented in 12–15 sessions over the course of 12 weeks. Originally developed for use in an individual format, it has been successfully adapted for use in group settings (Kaskutas et al, 2009). This approach is most often used in outpatient settings, but in South Africa is mainly integrated into Minnesota model-oriented inpatient programmes. The behavioural, spiritual, and cognitive principles of TSF and the Minnesota model are rooted in the 12 steps and traditions that are the foundation of 12-step fellowships such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) (McGovern & Carroll, 2003; Nowinski, 2000).

More specifically, TSF is designed to increase the likelihood of an individual becoming affiliated with, and actively involved in, 12-step support groups and thereby achieving

abstinence from substance use (McGovern & Carroll, 2003). TSF therapy has three goals for its clients:

- Facilitate acceptance, which includes understanding that addiction is a chronic, progressive disease over which the client has no control, that the client's life has become unmanageable due to their substance use, and that abstinence from substance use is the only solution
- Facilitate surrender, which involves giving oneself over to a higher power, and accepting the traditions and guidance of the 12-step fellowship and support of other recovering individuals
- To facilitate active involvement in 12-step support groups and related activities (McGovern & Carroll, 2003; Nowinski; 1997; Nowinski, 2000).

To achieve these goals, the TSF facilitator helps the client assess the severity of his/her substance use and identify the need for abstinence; explains the concepts, principles and traditions of the 12-step fellowships; actively supports and enables initial entry into the relevant 12-step fellowship; and encourages continued involvement in the fellowship through fellowship-related activities. Each TSF session follows a set format and has a specific topic. Every TSF session ends with the facilitator assigning individualised recovery tasks to the client, which need to be completed before the next session (McGovern & Carroll, 2003; Nowinski; 1997; Nowinski, 2000).

There is a large body of evidence supporting the effectiveness of TSF. For example, a preliminary trial of TSF with polysubstance-abusing individuals found that individuals who received TSF had significantly reduced their drug intake compared to those assigned to the treatment-as-usual condition (Hayes et al, 2004). Similarly, a controlled trial of a group-format TSF programme found that individuals assigned to this programme had significantly better abstinence rates and lower levels of alcohol and drug use than individuals assigned to the control group (Kastukas et al, 2009). The most compelling evidence for the effectiveness of TSF comes from Project MATCH, a multi-site randomised trial comparing the effectiveness of MET, RP and TSF. TSF was found to be more effective than no-treatment control conditions and as effective as, but not superior to, RP and MET treatment approaches (Project MATCH Research Group, 1997). In addition, individuals

Box 18.5: Types of 12-step support groups in South Africa

- *Alcoholics Anonymous (AA)* – for people who think they have a drinking problem and have a desire to stop
- *AlAnon Family Groups* – for people who have a family member or friend who has a problem with alcohol
- *Alateen* – for teenagers affected by parents' drinking
- *Narateen* – for teenagers affected by parents' drug use
- *NarAnon Family Groups* – for people who have a family member or friend who has a problem with drugs
- *Narcotics Anonymous (NA)* – for people who think they have a drug problem and have a desire to stop (http://www.na.org.za/)

attending TSF reported more days of 12-step fellowship attendance, a marker for sustained recovery (Moos et al, 2007) than individuals in the other conditions (Carroll et al, 1998; Carroll et al, 2000).

Continuing care for substance use disorders

As substance dependence is understood to be chronic and relapsing disorder, involvement in continued care services after completion of a primary treatment episode is a widely accepted evidence-based treatment guideline (Gossop et al, 2007; McGovern & Carroll, 2003; NIDA 1999; Ouimette et al, 1998). Continuing care services refer to the provision of ongoing support and counselling after an individual has completed a structured treatment programme and no longer requires services at the intensity needed during primary treatment (Brown et al, 2001). The primary goal of these services is to maintain the positive progress made during treatment by providing individuals with additional tools needed to lead a pro-social, drug-free lifestyle and avoid relapse to substance use (Gossop et al, 2007).

In South Africa, these services are generally provided by:

- Treatment providers who provide lower-intensity supportive counselling to clients who complete their programme
- 12-step-oriented halfway houses (secondary care) and sober living establishments (tertiary care) that provide low-intensity support services
- Self-help support groups in community settings that consist of individuals at various stages of recovery who act as a source of support to each other. As self-help groups are the most common and accessible form of continuing care in the country, they are described in more detail below.

In South Africa, the 12-step support groups are the most common type of self-help support group available. These abstinence-oriented groups are based on the principles of Alcoholics Anonymous (AA) and are found worldwide. They provide support for the individual with the alcohol or drug problem via their 12-step programme. There are various derivatives of these groups available, including those that provide support services for families affected by alcohol and drugs (see Box 18.5 for an outline of some of the 12-step groups available in the country).

These 12-step groups are located within local communities and provide an abstinence-oriented social support network which aids individuals in maintaining their sobriety. The groups use standard meeting formats and literature, are non-religious and free of charge (Gossop et al, 2007).

The benefits that active participation in 12-step support groups holds for the maintenance of treatment outcomes have been extensively documented. Numerous controlled trials have reported that individuals with post-treatment involvement in 12-step support groups had better long-term treatment outcomes than individuals with no involvement in these groups (Fiorentine, 1999; Fiorentine & Hillhouse, 2000; Humphreys et al, 1999; Moos et al, 2001). In addition, studies have shown that the greater the individual's involvement in the 12-step programme, the greater the benefits (Ouimette et al, 1998). Also, length of 12-step group membership is positively associated with better substance use outcomes (Humphreys, 2004).

Conclusion

It is clear that there is an urgent need to improve the availability of affordable treatment options in South Africa. The findings from various studies point to various quality improvements that can be made to South African treatment services. These include improving:

- Access to treatment through the use of mobile outpatient clinics and service quality improvement initiatives
- The integration of mental health and substance abuse services through the use of integrated care networks and by encouraging greater involvement of the DOH in the delivery of substance abuse treatment services
- Improving length of stay in treatment by strengthening clients' abstinence-oriented support networks and providing clients with stepped-down care options
- Improving treatment outcomes by ensuring clients engage in continuing care services.

In addition, policy frameworks need to be adopted on a national and regional level on the provision of services that utilise pharmacological treatment approaches, including substitution prescribing for opioid dependence. Treatment standards need to be defined and mechanisms set up for the accreditation of practitioners and institutions, as well as the monitoring of standards. Quality improvement initiatives also should focus on training service providers to deliver evidence-based psycho-social treatment, as outlined in this chapter.

From this discussion it is clear that a large amount of work needs to be done to improve the quality of treatment in South Africa. Efforts to improve service quality can be aided by developing a standardised service quality monitoring system for use in South African substance abuse services. Such a system would provide a foundation for evidence-based quality improvement enterprises and would allow for the impact of these enterprises on treatment outcomes to be examined.

References

Addolorato, G., Caputo, F., Capristo, E., Domenicali, M., Bernardi, M., Janiri, L., Agabio, R., Colombo, G., Gessa, G.L. & Gasbarrini, G. (2002). Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. *Alcohol and Alcoholism*, 37(5): 504–508.

Addolorato, G., Leggio, L., Cardone, S., Ferrulli, A. & Gasbarrini, G. (2009). Role of the GABA(B) receptor system in alcoholism and stress: focus on clinical studies and treatment perspectives. *Alcohol*, 43(7):559–63.

Addolorato, G., Leggio, L., Ferrulli, A., Cardone, S., Vonghia, L., Mirijello, A., Abenavoli, L., D'Angelo, C., Caputo, F., Zambon, A., Haber, P.S. & Gasbarrini, G. (2007). Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet*, 370(9603):1915–22.

Amato, L., Davoli, M., Minozzi, S., Ali, R. & Ferri, M. (2005). Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst. Rev.: CD003409.

Amato, L., Minozzi, S., Davoli, M., Vecchi, S., Ferri, M.M. & Mayet, S. (2008a). Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Cochrane Database Syst. Rev.: CD005031.

Amato, L., Minozzi, S., Davoli, M., Vecchi, S., Ferri, M.M. & Mayet S. (2008b). Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database Syst. Rev.: CD004147.

Amato, L., Minozzi, S., Pani, P.P. & Davoli, M. (2007). Antipsychotic medications for cocaine dependence. Cochrane Database Syst. Rev.: CD006306.

American Psychiatric Association. (2005). *Diagnostic and Statistical Manual of Mental Disorders. DSM-IV Task Force and Working Group*. 4th edition (text revision). Washington, DC, American Psychiatric Association.

Anton, R.F., O'Malley, S.S., Ciraulo, D.A., Cisler, R.A., Couper, D., Donovan, D.M., Gastfriend, D.R., Hosking, J.D., Johnson, B.A., LoCastro, J.S., Longabaugh, R., Mason, B.J., Mattson, M.E., Miller, W.R., Pettinati, H.M., Randall, C.L., Swift, R., Weiss, R.D., Williams, L.D. & Zweben, A. (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *Journal of the American Medical Association*, 295(17):2003–17.

Apodaca, T.R. & Longabaugh, R. (2009). Mechanisms of change in motivational interviewing: a review and preliminary evaluation of the evidence. *Addiction*, 104(5):705–15.

Ball, S.A., Martino, S., Nich, C., Frankforter, T.L., Van Horn, D., Crits-Christoph, P., Woody, G.E., Obert, J.L., Farentinos, C. & Carroll, K.M. (2009). Site matters: multisite randomized trial of motivational enhancement therapy in community drug abuse clinics. *Journal of Consulting and Clinical Psychology*, 77(2):336–45.

Barry, D.T., Irwin, K.S., Jones, E.S., Becker, W.C., Tetrault, J.M., Sullivan, L.E., Hansen, H, O'Connor, P.G., Schottenfeld, R.S. & Fiellin, D.A. (2009). Integrating buprenorphine treatment into office-based practice: a qualitative study. *Journal of General Internal Medicine*, 24(2):218–25.

Benegal, V., Chand, P.K. & Obot, I.S. (2009). Packages of care for alcohol use disorders in low- and middle-income countries. *PLoS Medicine*, 6(10):e1000170.

Bickel, W.K., Stitzer, M.L., Bigelow, G.E., Liebson, I.A., Jasinski, D.R. & Johnson, R.E. (1988). A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts. *Clinical Pharmacology & Therapeutics*, 43(1):72–78.

Birkhead, G.S., Klein, S.J., Candelas, A.R., O'Connell, D.A., Rothman, J.R., Feldman, I.S., Tsui, D.S., Cotroneo, R.A. & Flanigan, C.A. (2007). Integrating multiple programme and policy approaches to hepatitis C prevention and care for injection drug users: a comprehensive approach. *International Journal of Drug Policy*, 18(5):417–25.

Blakely, T.J. & Dziadosz, G.M. (2008.) Case management and social role theory as partners in service delivery. *Care Management Journal*, 9(3):106–12.

Bouza, C., Angeles, M., Muñoz, A. & Amate, J.M. (2004). Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction*, 99(7):811–28.

Branson, B.M., Handsfield, H.H., Lampe, M.A., Janssen, R.S., Taylor, A.W., Lyss, S.B., Clark, J.E.; Centers for Disease Control and Prevention (CDC). (2006). Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health care settings. *Morbidity and Mortality Weekly Report Recommendations and Reports*, 55(RR-14):1–17.

Brown, B.S., O'Grady, K.E., Battjes, R.J., Farrell, E.V., Smith, N.P. & Nurco D.N. (2001). Effectiveness of a stand-alone aftercare program for drug-involved offenders. *Journal of Substance Abuse Treatment*, 21(4):185–92.

Cahill, K., Stead, L.F. & Lancaster, T. (2008). Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst. Rev.: CD006103.

Carrieri, M.P., Amass, L., Lucas, G.M., Vlahov, D., Wodak, A. & Woody, G.E. (2006). Buprenorphine use: the international experience. *Clinical Infectious Diseases*, 43(Suppl. 4): S197–S215.

Carroll, K.M. (1996). Relapse prevention as a psychosocial treatment: a review of controlled clinical trials. *Experimental and Clinical Psychopharmacology*, 4(1):46–54.

Carroll, K.M., Connors, G.J., Cooney, N.L., DiClemente, C.C., Donovan, D.M., Kadden, R.R., Longabaugh, R.L., Rounsaville, B.J., Wirtz, P.W. & Zweben, A. (1998). Internal validity of Project MATCH treatments: discriminability and integrity. *Journal of Consulting and Clinical Psychology*, 66(2):290–303.

Carroll, K.M., Martino, S., Ball, S.A., Nich, C., Frankforter, T., Anez, L.M., Paris, M., Suarez-Morales, L., Szapocznik, J., Miller, W.R., Rosa, C., Matthews, J. & Farentinos, C. (2009). A multisite randomized effectiveness trial of motivational enhancement therapy for Spanish-speaking substance users. *Journal of Consulting and Clinical Psychology*, 77(5):993–99.

Carroll, K.M, Nich, C., Ball, S.A., McCance, E., Frankforter, T.L. & Rounsaville, B.J. (2000). One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: sustained effects of treatment. *Addiction*, 95(9):1335–49.

Cleary, M., Hunt, G.E., Matheson, S. & Walter, G. (2009). Psychosocial treatments for people with co-occurring severe mental illness and substance misuse: systematic review. *Journal of Advanced Nursing*, 65(2):238–58.

Connock, M., Juarez-Garcia, A., Jowett, S., Frew, E., Liu, Z., Taylor, R.J., Fry-Smith, A., Day, E., Lintzeris, N., Roberts, T., Burls, A. & Taylor, R.S. (2007). Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *International Journal of Technology Assessment in Health Care*, 11(9):i–iv.

Craig, T.K., Johnson, S., McCrone, P., Afuwape, S., Hughes, E., Gournay, K., White, I., Wanigaratne, S., Leese, M. & Thornicroft, G. (2008). Integrated care for co-occurring disorders: psychiatric symptoms, social functioning, and service costs at 18 months. *Psychiatric Services*, 59(3):276–82.

Darke, S., Ross, J. & Teesson, M. (2007). The Australian Treatment Outcome Study (ATOS): what have we learnt about treatment for heroin dependence? *Drug and Alcohol Review*, 26(1):49–54.

Darke, S., Ross, J., Teesson, M., Ali, R., Cooke, R., Ritter, A. & Lynskey, M. (2005). Factors associated with 12 months continuous heroin abstinence: findings from the Australian Treatment Outcome Study (ATOS). *Journal of Substance Abuse Treatment*, 28(3):255–63.

Day, E., Ison, J. & Strang, J. (2005). Inpatient versus other settings for detoxification for opioid dependence. Cochrane Database Syst. Rev.: CD004580.

De Sousa, A.A. & De Sousa, A. (2004). A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence. *Alcohol and Alcoholism*, 39(6):528–31.

De Sousa, A.A. & De Sousa, A. (2005). An open randomized study comparing disulfiram and acamprosate in the treatment of alcohol dependence. *Alcohol and Alcoholism*, (40):545–48.

De Sousa, A.A., De Sousa, J. & Kapoor, H. (2008a). An open randomized trial comparing disulfiram and topiramate in the treatment of alcohol dependence. *Journal of Substance Abuse Treatment*, 34(4):460–63.

De Sousa, A.A., De Sousa, J. & Kapoor, H. (2008b). An open randomized trial comparing disulfiram and topiramate in the treatment of alcohol dependence. *Journal of Substance Abuse Treatment*, 34(4):460–63.

Douaihy, A., Stowell, K.R., Park, T.W. & Daley, D.C. (2007). Relapse prevention: clinical strategies for substance use disorders. In K. Witkiewitz & G.A. Marlatt (eds). *Therapist's Guide to Evidence-Based Relapse Prevention*. London: Elsevier; pp 37–71.

Elkashef, A.M., Vocci, F., Hanson, G., White, J., Wickes, W. & Tiihonen, J. (2008a). Pharmacotherapy of methamphetamine addiction: an update. *Substance Abuse*, 29(3):31–49.

Elkashef, A.M., Rawson, R.A., Anderson, A.L., Li, S.H., Holmes, T., Smith, E.V., Chiang, N., Kahn, R., Vocci, F., Ling, W., Pearce, V.J., McCann, M., Campbell, J., Gorodetzky, C., Haning, W, Carlton, B, Mawhinney, J. & Weis, D. (2008b). Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacology*, 33(5):1162–70.

Fakier, N. & Myers, B. (2008). *Audit of Substance Abuse Treatment Facilities in Free State, Limpopo, Mpumalanga, North West and Northern Cape (2007–2008)*. Technical report. South African Medical Research Council.

Farrell, M., Gowing, L., Marsden, J., Ling, W. & Ali, R. (2005). Effectiveness of drug dependence treatment in HIV prevention. *International Journal of Drug Policy*, 16(Suppl. 1): S67–S75.

Fiorentine, R. (1999). After drug treatment: are 12-step programs effective in maintaining abstinence? *American Journal of Drug & Alcohol Abuse*, 25(1):93–116.

Fiorentine, R. & Hillhouse, M.P. (2000). Drug treatment and 12-step program participation: the additive effects of integrated recovery activities. *Journal of Substance Abuse Treatment*, 18(1):65–74.

Fleming, M.F., Manwell, L.B., Kraus, M., Isaacson, J.H., Kahn, R. & Stauffacher, E.A. (1999). Who teaches residents about the prevention and treatment of substance use disorders? A national survey. *The Journal of Family Practice*, 48(9):725–29.

Fuller, R.K., Branchey, L., Brightwell, D.R., Derman, R.M., Emrick, C.D., Iber, F.L., James, K.E., Lacoursiere, R.B., Lee, K.K. & Lowenstam, I. (1986a). Disulfiram treatment of alcoholism. A Veterans Administration cooperative study. *Journal of the American Medical Association*, 256(11):1449–55.

Galloway, G.P., Marinelli-Casey, P., Stalcup, J., Lord, R.H., Christian, D., Cohen, J., Reiber, C. & Vandersloot, D. (2000). Treatment-as-usual in the methamphetamine treatment project. *Journal of Psychoactive Drugs*, 32(2):165–75.

Garbutt, J.C. & Flannery, B. (2007). Baclofen for alcoholism. *Lancet*, 370(9603):1884–85.

Garbutt, J.C., Kampov-Polevoy, A., Flannery, B., Kalka-Juhl, L. & Gallop, R. (2007). Placebo-controlled trial of baclofen in alcohol dependence. Research Society on Alcoholism Annual Meeting, Chicago, Illinois.

Gianoulakis, C. (2009). Endogenous opioids and addiction to alcohol and other drugs of abuse. *Current Topics in Medicinal Chemistry*, 9(11):999–1015.

Gossop M. (2006). *Treating Drug Misuse Problems: Evidence of Effectiveness*. London: National Treatment Agency for Substance Misuse.

Gossop, M., Battersby, M. & Strang, J. (1991). Self-detoxification by opiate addicts. A preliminary investigation. *British Journal of Psychiatry*, 159:208–12.

Gossop, M., Johns, A. & Green, L. (1986). Opiate withdrawal: inpatient versus outpatient programmes and preferred versus random assignment to treatment. *British Medical Journal (Clinical Research Edition)*, 293(6539):103–104.

Gossop, M., Marsden, J., Stewart, D. & Kidd, T. (2003). The National Treatment Outcome Research Study (NTORS): 4–5 year follow-up results. *Addiction*, 98(3):291–303.

Gossop, M., Stewart, D., Browne, N. & Marsden, J. (2002). Factors associated with abstinence, lapse or relapse to heroin use after residential treatment: protective effect of coping responses. *Addiction*, 97(10):1259–67.

Gossop, M., Stewart, D. & Marsden, J. (2007). Attendance at Narcotics Anonymous and Alcoholics Anonymous meetings, frequency of attendance and substance use outcomes after residential treatment for drug dependence: a 5-year follow-up study. *Addiction*, 103(1):119–25.

Gowing, L., Ali, R. & White, J.M. (2009a). Buprenorphine for the management of opioid withdrawal. Cochrane Database Syst. Rev.: CD002025.

Gowing, L., Farrell, M., Ali, R. & White, J.M. (2009b). Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst. Rev.: CD002024.

Gowing, L., Farrell, M., Bornemann, R., Sullivan, L. & Ali, R. (2008). Substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Database Syst. Rev.: CD004145.

Grella, C.E., Etheridge, R.M., Joshi, V. & Anglin, M.D. (2000). Delivery of HIV risk reduction services in drug treatment programs. *Journal of Substance Abuse Treatment*, 19(3): 229–37.

Grella, C.E. & Stein, J.A. (2006). Impact of program services on treatment outcomes of patients with comorbid mental and substance use disorders. *Psychiatric Services*, 57(7):1007–15.

Hayes, S.C., Wilson, K.G., Gifford, E.V., Bissett, R., Piasecki, M., Batten, S.V., Byrd, M. & Gregg, V. (2004). A preliminary trial of twelve-step facilitation and acceptance and commitment therapy with polysubstance-abusing methadone-maintained opiate addicts. *Behavior Therapy*, 35(4):667–88.

Herman, A.A., Stein, D.J., Seedat, S., Heeringa, S.G., Moomal, H. & Williams, D.R. (2009). The South African Stress and Health (SASH) Study: 12-month and lifetime prevalence of common mental disorders. *South African Medical Journal*, 99(5): 339–44.

Hser, Y.I., Evans, E., Huang, D. & Anglin, M.D. (2004). Relationship between drug treatment services, retention and outcomes. *Psychiatric Services*, 55(7):767–74.

Hubbard, R.L, Craddock, S.G. & Anderson, J. (2003). Overview of 5-year followup outcomes in the drug abuse treatment outcome studies (DATOS). *Journal of Substance Abuse Treatment*, 25(3):125–34.

Huber, A., Ling, W., Shoptaw, S., Gulati, V., Brethen, P. & Rawson, R. (1997). Integrating treatments for methamphetamine abuse: a psychosocial perspective. *Journal of Addictive Diseases*, 16(4):41–50.

Huber, A., Lord, R.H., Gulati, V., Marinelli-Casey, P., Rawson, R.A. & Ling, W. (2000). The CSAT methamphetamine treatment project: research design accommodations for 'real world' application. *Journal of Psychoactive Drugs*, 32(2):149–56.

Hughes, J.R., Stead, L.F. & Lancaster, T. (2007). Antidepressants for smoking cessation. Cochrane Database Syst. Rev.: CD000031.

Humphreys, K. (2004). *Circles of Recovery: Self-help Organisations for Addictions*. Cambridge: Cambridge University Press.

Humphreys, K., Dearmin, P., Moos, R. & Finney, J. (1999). A comparative evaluation of substance abuse treatment: V treatment can enhance the effectiveness of self-help groups. *Alcoholism: Clinical and Experimental Research*, 23(3):558–63.

Johnson, B.A., Ait-Daoud, N., Bowden, C.L., DiClemente, C.C., Roache, J.D., Lawson, K., Javors, M.A. & Ma, J.Z. (2003). Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet*, 361(9370):1677–85.

Johnson, B.A., Rosenthal, N., Capece, J.A., Wiegand, F., Mao, L., Beyers, K., McKay, A., Ait-Daoud, N., Anton, R.F., Ciraulo, D.A., Kranzler, H.R., Mann, K., O'Malley, S.S., Swift, R.M. (2007). Topiramate for treating alcohol dependence: a randomized controlled trial. *Journal of the American Medical Association*, 298(14):1641–51.

Johnson, B.A., Rosenthal, N., Capece, J.A., Wiegand, F., Mao, L., Beyers, K., McKay, A., Ait-Daoud, N., Addolorato, G., Anton, R.F., Ciraulo, D.A., Kranzler, H.R., Mann, K., O'Malley, S.S. & Swift, R.M. (2008). Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Archives of Internal Medicine*, 168(11):1188–99.

Jupp, B. & Lawrence, A.J. (2010). New horizons for therapeutics in drug and alcohol abuse. *Pharmacology & Therapeutics*, 125(1):138–68.

Kaskutas, L.A., Subbaraman, M.S., Witbrodt, J. & Zemore, S.E. (2009). Effectiveness of Making Alcoholics Anonymous Easier: a group format 12-step facilitation approach. *Journal of Substance Abuse Treatment*, 37(3):228–23.

Kenna, G.A., Lomastro, T.L., Schiesl, A., Leggio, L. & Swift, R.M. (2009). Review of topiramate: an antiepileptic for the treatment of alcohol dependence. *Current Drug Abuse Reviews*, 2(2):135–42.

Kleber, H.D. (1996). Outpatient detoxification from opiates. *Primary Psychiatry*, 3(9):42–52.

Koob G.F. (2009). Neurobiological substrates for the dark side of compulsivity in addiction. *Neuropharmacology*, 56(Suppl. 1):18–31.

Koob, G.F. & Le Moal, M. (2008). Addiction and the brain antireward system. *Annual Review of Psychology*, 59:29–53.

Kraemer, K.L, Mayo-Smith, M.F. & Calkins, D.R. (2003). Independent clinical correlates of severe alcohol withdrawal. *Substance Abuse*, 24(4):197–209.

Kranzler, H.R. & Van, K.J. (2001). Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. *Alcoholism: Clinical & Experimental Research*, 25(9):1335–41.

Laaksonen, E., Koski-Jannes, A., Salaspuro, M., Ahtinen, H. & Alho, H. (2008a). A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. *Alcohol and Alcoholism*, 43(1):53–61.

Lott, D.C., Strain, E.C., Brooner, R.K., Bigelow, G.E. & Johnson, R.E. (2006). HIV risk behaviours during pharmacologic treatment for opioid dependence: a comparison of levomethadyl acetate, buprenorphine, and methadone. *Journal of Substance Abuse Treatment*, 31(2):187–94.

Mammen, K. & Bell, J. (2009). The clinical efficacy and abuse potential of combination buprenorphine-naloxone in the treatment of opioid dependence. *Expert Opinion on Pharmacotherapy*, 10(15):2537–44.

Mann, K., Lehert, P. & Morgan, M.Y. (2004). The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. *Alcoholism: Clinical & Experimental Research*, 28(1):51–63.

Marlatt, G. & Gordon, J.R. (1985). *Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors*. New York: Guilford Press.

Mattick, R.P., Breen, C., Kimber, J. & Davoli. M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst. Rev.: CD002209.

Mattick, R.P & Hall, W. (1996). Are detoxification programmes effective? *Lancet*, 347(8994):97–100.

Mattick, R.P., Kimber, J., Breen, C. & Davoli, M. (2008). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst. Rev.: CD002207.

Mayo-Smith, M.F. (1997). Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. *Journal of the American Medical Association*, 278(2):144–51.

Mayo-Smith, M.F., Beecher, L.H., Fischer, T.L., Gorelick, D.A., Guillaume, J.L., Hill, A., Jara, G., Kasser, C. & Melbourne, J. (2004). Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Archives of Internal Medicine*, 164(13):1405–12.

McGovern, M.P. & Carroll, K.M. (2003). Evidence-based practices for substance use disorders. *Psychiatric Clinics of North America*, 26(4):991–1010.

Miguez-Burbano, M.J., Ashkin, D., Rodriguez, A., Duncan, R., Pitchenik, A., Quintero, N., Flores, M. & Shor-Posner, G. (2005). Increased risk of *Pneumocystis carinii* and community-acquired pneumonia with tobacco use in HIV disease. *International Journal of Infectious Diseases*, 9(4):208–17.

Miguez-Burbano, M.J., Burbano, X., Ashkin, D., Pitchenik, A., Allan, R., Pineda, L., Rodriguez, N. & Shor-Posner, G. (2003). Impact of tobacco use on the development of opportunistic respiratory infections in HIV seropositive patients on antiretroviral therapy. *Addiction Biology*, 8(1): 39–43.

Miller, N.S., Sheppard, L.M., Colenda, C.C. & Magen, J. (2001). Why physicians are unprepared to treat patients who have alcohol- and drug-related disorders. *Academic Medicine*, 76(5):410–18.

Miller, P. (2009). *Evidence-based Addiction Treatment*. New York: Academic Press.

Miller, W.R. (1996). Motivational interviewing: research, practice and puzzles. *Addictive Behaviors*, 21(6):835–42.

Miller, W.R. (2005). Motivational enhancement therapy. In M. Hersen & J. Rosqvist (eds). *Encyclopedia of Behavior Modification and Cognitive Behavior Therapy. Volume 1. Adult Clinical Applications*. Thousand Oaks, CA: Sage Publications; pp 379–83.

Miller, W.R. & Rollnick, S. (2002). *Motivational Interviewing: Preparing People for Change*. 2nd edition. New York: Guilford Press.

Miller, W.R., Yahne, C.E. & Tonigan, J.S. (2003). Motivational interviewing in drug abuse services: a randomized trial. *Journal of Consulting and Clinical Psychology*, 71(4):754–63.

Minozzi, S., Amato, L., Davoli, M., Farrell, M., Lima Reisser, A.A., Pani, P.P., Silva, de L. M., Soares, B. & Vecchi, S. (2008). Anticonvulsants for cocaine dependence. Cochrane Database Syst. Rev.: CD006754.

Monte, R., Rabunal, R., Casariego, E., Bal, M. & Pertega, S. (2009). Risk factors for delirium tremens in patients with alcohol withdrawal syndrome in a hospital setting. *European Journal of Internal Medicine*, 20(7):690–94.

Moos, R.H. (2007). Theory-based active ingredients of effective treatments for substance use disorders. *Drug and Alcohol Dependence*, 88(2–3):109–21.

Moos, R.H., Schaefer, J., Andrassy, J. & Moos, B. (2001). Outpatient mental health care, self-help groups and patients' one-year treatment outcomes. *Journal of Clinical Psychology*, 57(3):273–87.

Myers, B. (2007). *Access to Substance Abuse Treatment for Historically Underserved Communities in the Cape Town Metropole*. Technical report. South African Medical Research Council.

Myers, B. (2010). Limited access to HIV risk reduction services in South African substance abuse treatment services. *Drugs: Education, Prevention & Policy*, 17(6):749–61.

Myers, B., Burnhams, N.H. & Fakier N. (2010). Monitoring and evaluation of substance abuse services in South Africa: implications for policy and practice. *International Journal of Mental Health and Addiction*, 8(4):557–65.

Myers, B. & Fakier, N. (2007). *Audit of Substance Abuse Treatment Facilities in KwaZulu-Natal and Gauteng, 2007*. Technical report. South African Medical Research Council.

Myers, B. & Fakier, N. (2009). Provision of mental health services in South African substance abuse treatment facilities. *International Journal of Mental Health and Addiction*, 7(3):441–49.

Myers, B., Fakier, N. & Louw. J. (2009). Stigma, treatment beliefs, and substance abuse treatment use in historically disadvantaged communities. *African Journal of Psychiatry*, 12(3):218–22.

Myers, B., Harker, N., Fakier, N., Kader, R. & Mazok, C. (2008). *A Review of Evidence-based Interventions for the Prevention and Treatment of Substance Use Disorders.* South African Medical Research Council.

Myers, B., Louw, J. & Fakier, N. (2008). Alcohol and drug abuse: removing structural barriers to treatment for historically disadvantaged communities in Cape Town. *International Journal of Social Welfare*, 17(2):156–65.

Myers, B. & Parry, C.D.H. (2005). Access to substance abuse treatment for Black South Africans: findings from audits of specialist substance abuse treatment facilities. *South African Psychiatry Review*, 8(1):15–19.

National Department of Social Development. (1997). White Paper on the Transformation of the Social Welfare System. Pretoria: Department of Social Development.

National Institute on Drug Abuse. (1999). *Principles of Drug Addiction Treatment. A Research-based Guide*. Washington, DC: National Institute of Health.

Nowinski, J. (2000). Twelve-step facilitation therapy. In K.M. Carroll (ed.). *Approaches to Drug Abuse Counselling*. Washington, DC: National Institute on Drug Abuse; pp 52–63.

Nowinski, J. & Baker, S. (1997). *The Twelve-Step Facilitation Handbook: A Systematic Approach to Early Recovery from Alcoholism and Addiction*. New York: Jossey-Bass.

Ntais, C., Pakos, E., Kyzas, P. & Ioannidis, J.P. (2005). Benzodiazepines for alcohol withdrawal. Cochrane Database Syst. Rev.: CD005063.

Obert, J.L., Hamilton Brown, A., Zweben, J., Christian, D., Delmhorst, J., Minsky, S., Morrisey, P., Vandersloot, D. & Weiner, A. (2005). When treatment meets research: clinical perspectives from the CSAT Methamphetamine Treatment Project. *Journal of Substance Abuse Treatment*, 28(3):231–37.

Obert, J.L., London, E.D. & Rawson, R.A. (2002). Incorporating brain research findings into standard treatment: an example using the Matrix Model. *Journal of Substance Abuse Treatment*, 23(2):107–13.

Ouimette, P.C., Moos, R.H. & Finney, J.W. (1998). Influence of outpatient treatment and 12-step group involvement on one-year substance abuse treatment outcomes. *Journal of Studies on Alcohol*, 59(5):513–22.

Padgett, D.K., Henwood, B., Abrams, C., Davis, A. (2008). Engagement and retention in services among formerly homeless adults with co-occurring mental illness and substance abuse: voices from the margins. *Psychiatric Rehabilitation Journal*, 31(3):226–33.

Palmstierna, T. (2001). A model for predicting alcohol withdrawal delirium. *Psychiatric Services*, 52(6):820–23.

Pani, P.P., Trogu, E., Vacca, R., Amato, L., Vecchi, S. & Davoli, M. (2010). Disulfiram for the treatment of cocaine dependence. Cochrane Database Syst. Rev.: CD007024.

Parran, T.V., Adelman, C.A., Merkin, B., Pagano, M.E., Defranco, R., Ionescu, R.A. & Mace, A.G. (2010). Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy. *Drug and Alcohol Dependence*, 106(1):56–60.

Parry, C.D.H. (1997). Alcohol, drug abuse, and public health. In D. Foster, M. Freeman & Y. Pillay (eds). *Mental Health Policy Issues for South Africa*. Medical Association of South Africa: pp. 290–315.

Parry, C.D.H. & Bennetts, A. (1998). *Alcohol Policy and Public Health in South Africa*. Cape Town: Oxford University Press.

Parry, C.D.H. & Pithey, A. (2006). Risk behaviour and HIV among drug using populations in South Africa. *African Journal of Drug and Alcohol Studies*, 5(2):139–56.

Parry, C.D.H., Plüddemann, A., Steyn, K., Bradshaw, D., Norman, R. & Laubscher, R. (2005). Alcohol use in South Africa: findings from the first Demographic and Health Survey (1998). *Journal of Studies on Alcohol*, 66(1):91–97.

Pasche, S., Myers, B., Adams, M.E. (in press). Factors associated with retention in alcohol and other drug treatment among disadvantaged communities in Cape Town, South Africa. *Journal of Studies on Alcohol and Drugs*.

Plüddemann, A., Dada, S., Williams, Y., Bhana, A., Pereira, T., Carelsen, A., Gerber, W., Rosslee, C., Parry, C. & Fourie D. (2009). *Monitoring Alcohol and Drug Abuse Treatment Admissions in South Africa. Feedback from the South African Community Epidemiology Network on Drug Use (SACENDU) project, Phase 25, July–December 2008*. South African Medical Research Council.

Project MATCH Research Group. (1997). Matching alcoholism treatments to client heterogeneity: Project MATCH post-treatment drinking outcomes. *Journal of Studies on Alcohol*, 58(1):7–29.

Rawson, R., Gonzales, R., Pearce, V., Marinelli-Casey, P., Ang, A. & Brummer, J. (2008). Methamphetamine dependence and human immunodeficiency virus risk behavior. *Journal of Substance Abuse Treatment*, 35(3):279–84.

Rawson, R.A., Marinelli-Casey, P.J. & Huber, A. (2002). A multi-site evaluation of treatment of methamphetamine dependence in adults. In J. Herrell & R.B. Straw (eds). *Conducting Multiple Site Evaluations in Real-World Settings*. Fairhaven, MA: American Evaluation Association; pp 73–87.

Rawson, R.A., Obert, J.L., McCann, M.J. & Marinelli-Casey, P. (1993). Relapse prevention strategies in outpatient substance abuse treatment. *Psychology of Addictive Behavior*, 7(2):85–95.

Rawson, R., Shoptaw, S., Obert, J.L., McCann, M., Hasson, A., Marinelli-Casey, P., Brethen, P. & Ling, W. (1995). An intensive outpatient approach for cocaine abuse: the Matrix model. *Journal of Substance Abuse Treatment*, 12(2):117–27.

Rosenberg, H. & Phillips, K.T. (2003). Acceptability and availability of harm-reduction interventions for drug abuse in American substance abuse treatment agencies. *Psychology of Addictive Behaviors*, 17(3):203–10.

Rösner, S., Leucht, S., Lehert, P. & Soyka, M. (2008). Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. *Journal of Psychopharmacology*, 22(1):11–23.

Saitz, R. & O'Malley, S.S. (1997). Pharmacotherapies for alcohol abuse. Withdrawal and treatment. Medical Clinics of North America, 81(4):881–907.

San, L., Cami, J., Fernandez, T., Olle, J.M., Peri, J.M. & Torrens, M. (1992). Assessment and management of opioid withdrawal symptoms in buprenorphine-dependent subjects. *British Journal of Addiction*, 87(1):55–62.

Schmitz, J.M., Oswald, L.M., Jacks, S.D., Rustin, T., Rhoades, H.M. & Grabowski, J. (1997). Relapse prevention treatment for cocaine dependence: group vs. individual format. *Addictive Behaviors*, 22(3):405–18.

Schuckit, M.A., Tipp, J.E., Reich, T., Hesselbrock, V.M. & Bucholz, K.K. (1995). The histories of withdrawal convulsions and delirium tremens in 1648 alcohol dependent subjects. *Addiction*, 90(10):1335–47.

Scott, L.J., Figgitt, D.P., Keam, S.J. & Waugh, J. (2005). Acamprosate: a review of its use in the maintenance of abstinence in patients with alcohol dependence. *CNS Drugs*, 19(5):445–64.

Shi, J., Zhao, L.Y., Epstein, D.H., Zhang, X.L. & Lu, L. (2007). Long-term methadone maintenance reduces protracted symptoms of heroin abstinence and cue-induced craving in Chinese heroin abusers. *Pharmacology Biochemistry & Behavior*, 87(1):141–45.

Silins, E., Sannibale, C., Larney, S., Wodak, A. & Mattick, R. (2008). Residential detoxification: essential for marginalised, severely alcohol- and drug-dependent individuals. *Drug and Alcohol Review*, 27(4):414–19.

Silva, de L.M., Farrell, M., Lima Reisser, A.A. & Soares, B. (2010). WITHDRAWN: Antidepressants for cocaine dependence. Cochrane Database Syst. Rev. (2): CD002950.

Simpson, D.D. (2004). A conceptual framework for drug treatment process and outcomes. *Journal of Substance Abuse Treatment*, 27(2):99–121.

Soares, B., Lima Reisser, A.A., Farrell, M.& Silva, de L.M. (2010). WITHDRAWN: Dopamine agonists for cocaine dependence. Cochrane Database Syst. Rev. (2): CD003352.

South Africa, Republic of. (2009). Prevention of and Treatment for Substance Abuse Act 70 of 2008. *Government Gazette*, 21 April 2009; 526:31250.

Srisurapanont, M. & Jarusuraisin, N. (2005). Opioid antagonists for alcohol dependence. Cochrane Database Syst. Rev.: CD001867.

Srisurapanont, M. & Jarusuraisin, N. & Kittirattanapaiboon, P. (2001). Treatment for amphetamine dependence and abuse. Cochrane Database Syst. Rev.: CD003022.

Stead, L.F. & Perera, R., Bullen, C., Mant, D. & Lancaster, T. (2008). Nicotine replacement therapy for smoking cessation. Cochrane Database Syst. Rev.: CD000146.

Stein, L.A.R., Colby, S.M., Barnett, N.P., Monti, P.M., Golembeske, C., Lebveau-Craven, R. & Miranda, R. (2006). Enhancing substance abuse treatment engagement in incarcerated adolescents. *Psychological Services*, 3(1):25–34.

Strathdee, S.A. & Sherman, S.G. The role of sexual transmission of HIV infection among injection and non-injection drug users. *Journal of Urban Health* 2003; 80(4 Suppl. 3): ii7–iii14.

Sullivan, J.T, Sykora, K., Schneiderman, J., Naranjo, C.A. & Sellers, E.M. (1989). Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *British Journal of Addiction*, 84(11):1353–57.

Sullivan, L.E. & Fiellin, D.A. (2008). Narrative review: buprenorphine for opioid-dependent patients in office practice. *Annals of Internal Medicine*, 148(9):662–70.

Thirthalli, J. & Chand, P.K. (2009). The implications of medication development in the treatment of substance use disorders in developing countries. *Current Opinion in Psychiatry*, 22(3):274–80.

Thomson, A.D., Cook, C.C., Touquet, R. & Henry, J.A. (2002). The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and emergency department. *Alcohol and Alcoholism*, 37(6):513–21.

Tiihonen, J., Kuoppasalmi, K., Fohr, J., Tuomola, P., Kuikanmaki, O., Vorma, H., Sokero, P., Haukka, J. & Meririnne, E. (2007). A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. *American Journal of Psychiatry*, 164(1): 160–62.

Trevor, A.J & Way, W.L. (1998). Sedative-hypnotic drugs. In B.G. Katzung. *Basic and Clinical Pharmacology*. 7th edition. Stamford, CT: Appleton & Lange; pp 354–60.

United Nations Office on Drugs and Crime (UNODC) and World Health Organization (WHO). (2008). Principles of Drug Dependence Treatment. Discussion Paper. Vienna & Geneva: UNODC & WHO.

Walsh, S.L & Eissenberg, T. (2003). The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. *Drug and Alcohol Dependence*, 70(Suppl. 2): S13–S27.

Wedam, E.F., Bigelow, G.E., Johnson, R.E., Nuzzo, P.A. & Haigney, M.C. (2007). QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Archives of Internal Medicine*, 167(22):2469–75.

Weich, L., Perkel, C., Van Zyl, N., Rataemane, S.T. & Naidoo. L. (2008). Medical management of opioid dependence in South Africa. *South African Medical Journal*, 98(4):280–83.

WHO. (2009). *Guidelines for Psychosocially Assisted Pharmacological Treatment of Opioid Dependence*. Geneva: World Health Organization.

Wilson, B.K., Elms, R.R. & Thomson, C.P. (1975). Outpatient vs hospital methadone detoxification: an experimental comparison. *International Journal of the Addictions*, 10(1):13–21.

Winstock, A.R., Lea, T. & Sheridan, J. (2009). What is diversion of supervised buprenorphine and how common is it? *Journal of Addictive Diseases*, 28(3):269–78.

Witkiewitz, K. & Marlatt, G.A. (2004). Relapse prevention for alcohol and drug problems: that was Zen, this is Tao. *American Psychologist*, 59(4):224–35.

Witkiewitz, K. & Marlatt, G.A. (2007). Overview of relapse prevention. In K. Witkiewitz & G.A. Marlatt (eds). *Therapist's Guide to Evidence-Based Relapse Prevention*. London: Elsevier; pp 3–17.

19 Substance abuse policy in South Africa

Crick Lund and Noxolo Hewana

Introduction

As other chapters in this volume have indicated, substance abuse is a major social problem in South Africa, and is associated with a substantial health burden and enormous personal, social and economic costs. The extent to which this problem is addressed depends in no small measure on the extent to which the South African government is willing to give priority to the problem, through a clearly formulated set of national policies and laws, which are subsequently implemented through strategic plans and budgets. Without these policies and laws, efforts are likely to be at best piecemeal, poorly coordinated and lacking in the political will required to mobilise the required social and economic resources.

This chapter provides a review of the historical and current policy and legislative framework for substance abuse in South Africa. It identifies some gaps in substance abuse policy in South Africa, and recommendations for how they could be addressed.

Substance abuse policy: conceptual issues

Public policy has been defined as 'a system of laws, regulatory measures, courses of action, and funding priorities concerning a given topic promulgated by a governmental entity or its representatives' (Kilpatrick, 2010). A policy, therefore, represents the stated intention by a government to address a particular social, political or economic issue. Policies can take a number of forms, from the proclamations of politicians to formally adopted documents which are the products of extensive stakeholder consultation and research. Various incentives can be created for the implementation of policies. For example, when linked to legislation, these policies can carry legal consequences when implementation fails. When linked to budgets or financial incentives, policies can carry rewards for those who successfully implement them. We use the term 'policy' in a broad sense to include both policy documents and legislation.

The extent to which a policy is appropriate and can be feasibly implemented depends on a number of factors. These can be understood within a broad framework for policy development and implementation (see Figure 19.1):

1. The development of policies relies on a number of processes, including the role of key stakeholders (Walt & Gilson, 1994) and the use of evidence (Haines & Victoria 2004). These policy development processes require needs assessments, consultation and negotiation with various stakeholders, and an assessment of options.

2. The vision, aims and objectives of a policy need to be feasible within the current resource constraints of a country or region.
3. In order to be implemented, policies need to move beyond abstract formulation and be translated into operational plans and programmes.
4. In order for these plans and laws to be implemented successfully, reliable systems need to be in place, such as networks of substance abuse treatment centres, a well-functioning education system for the implementation of prevention interventions, and a police force to curb the manufacture and supply of illicit substances.
5. Crucially, the implementation of policies relies on the buy-in and ownership of a number of stakeholders. In the substance abuse field this includes teachers, health workers, counsellors, police, correctional services staff, community leaders and, of course, those who use substances. A lack of ownership by such key stakeholders, or conflicting opinions regarding the solutions to problems of substance abuse, may lead to fragmented implementation (Flisher et al, 2007).

Several policy analysts have argued that social and health policy development and implementation processes seldom follow rational steps, such as problem identification, consensus building, policy formulation and implementation. More often, it is argued, policy development is a relatively random process, which accelerates when certain 'policy windows' are opened (Kingdon, 1984). According to this theory, it is only at the confluence of three streams (issues faced by society, alternatives that can potentially address these issues, and political events, or social and political pressures) that progress is made with policy development and implementation. Others have argued that transnational influence, domestic advocacy and the national political environment all influence the extent to which a particular issue becomes prominent on the policy agenda, rather than rational processes (Shiffman 2007).

In the field of substance abuse, a crucial challenge is that policy formulation and implementation require the collaboration of a number of governmental sectors, such as health, education, social development and criminal justice. This immediately poses challenges regarding leadership: which government sector should lead the process of policy formulation? Which should commit resources to its implementation? And which is responsible for providing the various services required for the regulation and control of the supply of substances, and for prevention, treatment and rehabilitation?

Historical overview

In South Africa, many of these challenges are mirrored in the historical development and implementation of policies and laws related to substance abuse. This history is driven to varying degrees by a number of different government and civil society stakeholders, and by key developments associated with 'policy windows', such as those created by the end of apartheid and the advent of a democratic dispensation.

South Africa was a signatory to the United Nations (UN) Single Convention on Narcotic Drugs (1961), the 1970 Protocol and the UN Convention on Psychotropic Substances (1971). The South African government developed the Abuse of Dependence-Producing

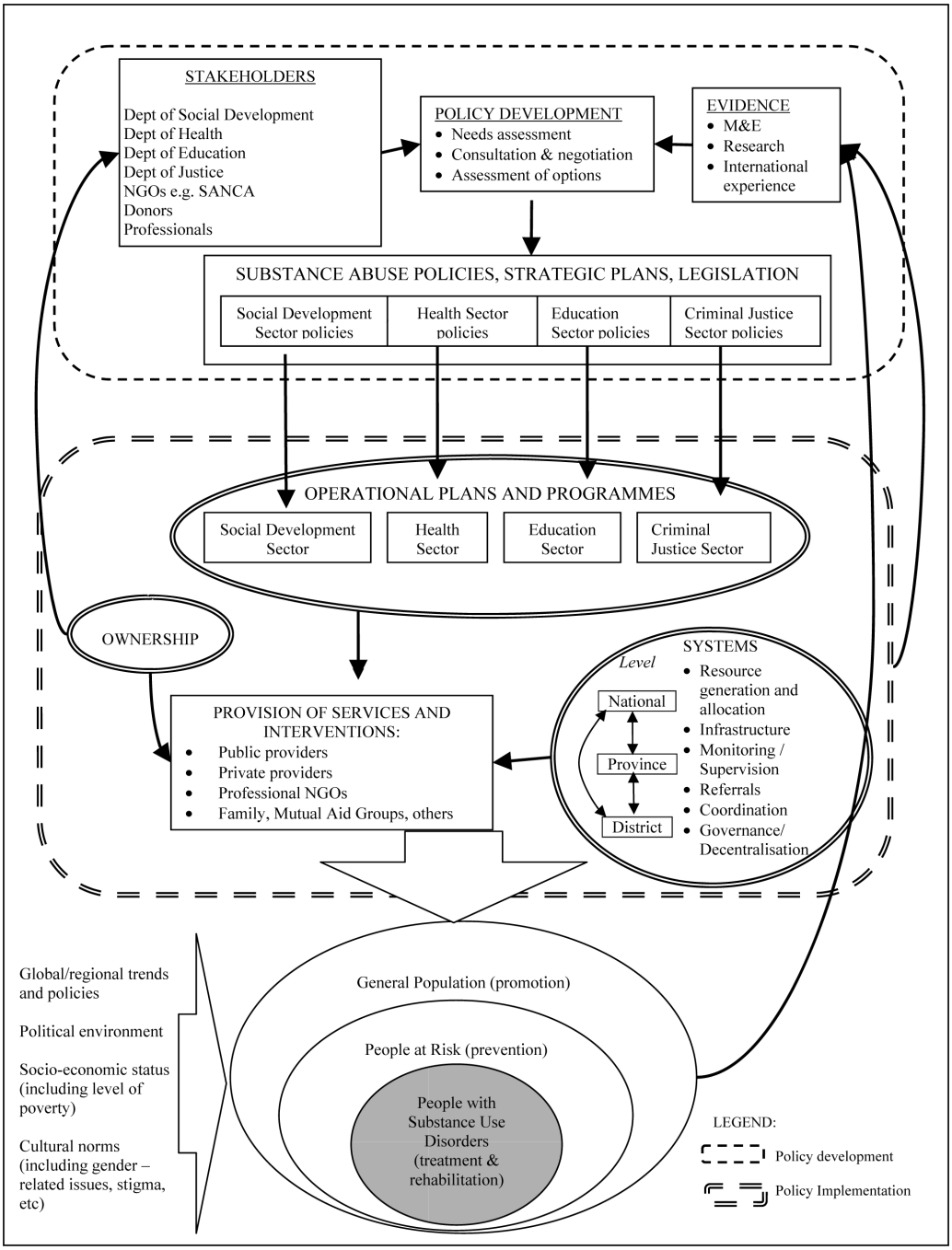

Figure 19.1: Framework for substance abuse policy development and implementation in South Africa
(Adapted from Flisher et al, 2007)

Substances and Rehabilitation Centres Act in 1971, which was amended in 1973. The Act created penalties for minor dealing and possession of drugs, such as imprisonment for a period of not less than five years, but not exceeding 15 years. In the 1980s, South Africa became part of a major international network to combat drug trafficking when the country joined the United Nations Office of Drug Traffic Laws. The focus was on illicit drugs such as heroin and cocaine, which became a threat as expanding networks of drug trafficking, principally from Nigeria, looked for new markets (Roman, Ahn-Redding & Simon, 2005).

The Prevention and Treatment of Drug Dependency Act (1992) established the first Drug Advisory Board (DAB) in 1993. The DAB's function was to advise the Minister of Welfare and Population Development on matters pertaining to alcohol and drug abuse and to 'plan, coordinate and promote measures relating to the prevention and combating of drug abuse and to the treatment of drug-dependent people' (Department of Welfare, 1999). The DAB was therefore a key attempt to develop a united government response to substance abuse in South Africa, in the late apartheid era.

The Drugs and Drug Trafficking Act (1992) focused on drug offences, including the possession or selling of cocaine, heroin or cannabis. All amphetamines and barbiturates were regarded as legal drugs which could be purchased in pharmacies. The age of criminal responsibility was 17; ages 12 to 16 were treated as juveniles, and ages 7 to 11 were treated as children. Crimes by youth under 17 years were handled by juvenile courts.

The Tobacco Products Control Act (1993) effectively made provision for designated smoking areas and restrictions on tobacco industry advertising, including picture health warnings on all cigarette boxes, the banning of smoking in cars in the presence of a child under 12 years, the restriction of entry to smoking areas for people under the age of 18 and increases in fines for smoking in public spaces.

After the demise of apartheid in 1994, more concerted efforts were made to address substance abuse issues in policy as policy 'windows' opened for broader political and social reform. In 1995 South Africa hosted a joint conference of the Southern African Development Community and the European Union to discuss drug trafficking. The conference adopted a regional protocol on reducing the drug trade in the southern African region (Roman, Ahn-Redding & Simon, 2005). This initiative was partly in response to broader contextual changes precipitated by the end of apartheid. The physical and economic isolation of the country under apartheid, strict monitoring of external borders and stringent internal controls had restricted access to drugs in South Africa. After 1994, reductions in external border controls, increased travel and trade, and the country's poorly resourced law enforcement agencies created new opportunities for drug cartels targeting the South African market (Myers, Louw & Fakier 2007).

Also in 1995, the Department of Health's Mental Health and Substance Abuse Committee recommended immediate involvement and full participation of the Department of Health in all aspects of prevention, treatment and rehabilitation of substance abuse. The committee also recommended the establishment of an intersectoral structure to facilitate cooperation between health and welfare sectors in the substance abuse area and the re-establishment of the Drug Advisory Board, as an entity that could facilitate such intersectoral collaboration.

The South African Community Epidemiology Network on Drug Use (SACENDU) was established in 1996 by the South African Medical Research Council (MRC) and the

Department of Psychology at the University of Durban-Westville with funding from the World Health Organization (WHO). SACENDU has been a key source of data that has informed many subsequent policy and legislation developments in South Africa (Parry et al, 2002).

The Tobacco Products Control Act was amended in 1999, with bans on all advertising and promotion of tobacco products, including sponsorship and free distribution of tobacco products. The Act restricts smoking in public places, including the workplace, restaurants, bars and public transport. The Act also stipulates penalties for transgressors of the law, and specifies the maximum permissible level of tar and nicotine. The regulations were implemented in 2001. The government proposed further amendments to the bill in 2007. These amendments aimed to bring the current law into compliance with the WHO Framework Convention on Tobacco Control.

The National Drug Master Plan (NDMP) was adopted in February 1999, to act as the barometer of the commitment and performance of the South African government and its citizens in the field of substance abuse. Aware of a history of fragmented leadership in substance abuse, the main aim of the NDMP was to form a united front of all stakeholders in the country, for joint action towards a society free of drug abuse and its related problems. As illustrated in Table 19.1, a wide range of stakeholders were involved in the development of the NDMP. The NDMP strives to implement holistic and affordable approaches to decrease the availability and use of drugs and to minimise the consequences associated with substance abuse in South Africa. Five areas of focus were identified, namely, crime, youth, community health and welfare, research and information dissemination, and international involvement. The NDMP outlines specific objectives pertaining to youth. It includes:

- Encouraging youth to refrain from drug use
- Ensuring that schools offer effective drug education programmes
- Increasing parents', educators' and school governing bodies' awareness of drug misuse
- Developing public education strategies for youth on both a national and local level
- Ensuring that high-risk youth or youth involved in drug misuse have access to counselling, advice, treatment and rehabilitation services.

The NDMP also evoked the provisions of the Constitution, which grants citizens the right to have their dignity respected and protected, and the right to life, freedom and security. To realise these rights, the government committed itself in the NDMP to reducing the supply of illegal drugs and the demand for such drugs through a wide range of measures and programmes.

As a consequence of the NDMP, the Central Drug Authority (CDA) was established in 2000, comprising governmental appointees and experts from the non-governmental sector. A key innovation of the CDA was that it included representatives of a wide range of sectors and stakeholders, was answerable to Parliament, and therefore was intended to reach across sectors in its mandate. The CDA was established with the understanding that the current NDMP would be reviewed every five years, and amended and submitted for approval to Cabinet when necessary. However, it was understood that the CDA would not replace the responsibilities of various government departments and NGOs.

Table 19.1: Current substance abuse policy, legislation and strategic plans in South Africa

NAME OF POLICY/LAW	DATE	AIM	SCOPE	STAKEHOLDERS CONSULTED
Drugs and Drug Trafficking Act	1992	1. To end drug trafficking by law enforcement 2. To fight use and possession of illicit drugs	Defines illegal acts related to drug use and trafficking, offences, penalties, presumptions and forfeiture of proceeds of drug trafficking	United Nations Office of Drug Crime; Medical Research Council; Correctional Services; Department of Health and Welfare
Tobacco Products Control Act	1993, amended in 1999 and 2007	1. To prohibit or restrict smoking in public places 2. To regulate the sale and advertising of tobacco products	Provides measures to control the smoking of tobacco products, to regulate advertising and sponsorship and to specify packaging of tobacco products (such as health warnings)	Departments of Health, Trade and Industry, Agriculture and Land Affairs, Finance, Justice and Correctional Services; WHO; Tobacco industry; Director of Public Prosecutions
National Drug Master Plan	1999, revised in 2006	To bring about the reduction of substance abuse and its related harmful consequences in five priority areas: Crime, Youth, Community health and welfare, Research and information dissemination, and International involvement	Provides a vision, priorities and objectives; describes the composition and functions of the CDA, local Drug Action Committees and provincial Drug Forums; articulates the roles and responsibilities of all the major sectors involved in substance abuse	Office of the Attorney-General; SA Alliance for Prevention of Substance Abuse; Departments of Welfare, Health, Education, Foreign Affairs, Correctional Services and Justice; SA Narcotics Bureau; SARS; SANCA; MRC; HSRC; CSIR; National Crime prevention strategy; and Medicines Control Council
National Policy on Drug Abuse Management in Schools	2002	1. To prevent manage and treat drug use, misuse and dependency in schools 2. To develop a safe and supportive school environment that values human dignity 3. To educate learners about drug use and abuse	Sets out the Department of Education's Guiding Principles for substance abuse in schools. Provides recommendations for drug screening/testing, searches, education, prevention, interventions and school and institutional management plans. Alignment with the NDMP explicitly mentioned	Departments of Education, Health, Correctional services, Social Development; and the Council of provincial MECs for Education
Liquor Act	2003	1. To establish norms and standards in order to maintain economic unity within the liquor industry 2. To provide national standards for rendering services 3. To provide measures for cooperative government in the area of liquor regulation	Articulates the national liquor policy, including regulation of the manufacture and distribution of liquor and other substances; provides for registration of manufacturers and distributors of alcohol; provides measures for compliance, such as inspectors and warrants; describes offences and penalties; and provides for the establishment, composition and functions of the Liquor Policy Council	Minister of Trade and Industry and relevant MECs of the provinces; Departments of Agriculture, Social Development, Correctional Services, Arts and Culture, Labour; Home Affairs, and Safety and Security; Medicines Control Council; National Youth Commission

(*continued*)

Table 19.1: Current substance abuse policy, legislation and strategic plans in South Africa (continued)

NAME OF POLICY/LAW	DATE	AIM	SCOPE	STAKEHOLDERS CONSULTED
Prevention of and Treatment for Substance Abuse Act	2008	1. To provide a comprehensive national response for combating substance abuse 2. To provide mechanisms aimed at demand and harm reduction 3. To provide for the registration and establishment of treatment centres and halfway houses 4. To provide for the treatment and committal, treatment and rehabilitation of persons in treatment centres 5. To provide for the establishment of the Central Drug Authority	Provides strategies and principles for demand and harm reduction; outlines prevention and early intervention services, including stakeholder roles and responsibilities; provides guidelines and regulations for community-based inpatient, outpatient services, aftercare and reintegration services; describes the process for admission, transfer and referral to treatment centres; describes disciplinary interventions and appeal procedures; provides for the establishment of CDA and supporting structures	Departments of Social Development, Health, Education, Foreign Affairs, Correctional Services and Justice; SA Narcotics Bureau; SANCA; MRC; HSRC; CSIR; National Crime prevention strategy; Office of the Attorney General; SA Alliance for Prevention of Substance Abuse

With a view to taking up its sectoral responsibilities in response to the NDMP, the Department of Health addressed substance abuse in its Health Sector Strategic Framework (1999–2004). The targets of this framework were:

- To decrease alcohol/drug abuse by 10% by 2004 through decentralised treatment in general hospitals and rehabilitation programmes and campaigns
- Reduce the incidence of fetal alcohol syndrome (FAS) by 50% through implementing community-based programmes involving education and assistance to 'problem drinking'
- Have nurses trained in mental health and substance abuse in 50% of all health facilities, and thus integrate mental health and substance abuse and other health activities at all levels.

Substance Abuse Policy Guidelines were subsequently developed by the Department of Health in 2000, the aims of which were to:

- Prevent and manage substance abuse
- Raise awareness of substance abuse within the context of primary health care (PHC)
- Train and educate PHC practitioners to fully integrate substance abuse prevention/management with the PHC domain
- Develop community-based prevention/management models to reinforce positive behaviours that promote healthy lifestyles.

The Department of Social Development and the United Nations Office for Drug Control (UNODC) launched the 'Ke Moja' Project in 2005. A prevention programme that targets the youth, 'Ke Moja' means 'no thanks' and aims to inform and educate the public about the dangers of drugs, as well as to mobilise children and youth to say 'no' to substance

abuse. The youth Best-Practice Treatment Model was developed and training provided countrywide to facilitate roll-out of the model. The model proposes essential elements to be considered when offering treatment to youth in residential facilities. The pilot conducted in five government facilities showed positive results of minimum standards for in-patient treatment centres. These standards were meant to be used to transform service delivery in government facilities as a first priority, and to ensure that appropriate services are provided at these centres. They also have to set the framework for the registration of treatment centres run by civil society structures in the country. The government encouraged the registration of centres in terms of the Prevention and Treatment of Drug Dependency Act (1992).

The National Policy on Drug Abuse Management in Schools (2002) was adopted by the Department of Education to contribute towards effective prevention, management and treatment of drug use, misuse and dependency in educational institutions in South Africa. It is a policy framework that promotes the creation of a healthy learning/school environment and the provision of skill-based health education by appropriately trained teachers to prevent and reduce drug misuse and abuse. It sets forth relevant national laws and protections, but calls upon local school authorities to develop drug use, misuse and dependency management plans that reflect the needs and values of the school and its community, that are consistent, fair and rights-based and that seek above all the rehabilitation and continued schooling of students involved in drug-related incidents. The policy also seeks to develop a range of responses for managing drug-related incidents within the school, taking into account confidentiality, the nature of the incidents, the circumstances of the learners involved and the needs and safety of the school community. The policy aimed to build capacity by making professional development opportunities available for educators, especially those working with drug-related incidents.

The Liquor Act (2003), ratified in August 2004, aims to reduce the socio-economic and broad consequences of alcohol abuse and promote the development of a responsible and sustainable liquor industry. The Act stipulates that a person may not advertise alcohol with the intention to target or attract minors or sell or supply alcohol to a minor. A person supplying or selling alcohol must take suitable measures to determine whether or not a person is a minor. A minor may not falsely claim to be of age in order to purchase or access alcohol. A person may not make a false claim about a minor's age in order to persuade a person to sell or supply alcohol to a minor. A minor may not produce or import liquor, or supply liquor to another person. The parent or adult guardian of a minor, or a person responsible for overseeing a religious sacrament, may on occasion supply a small quantity of alcohol to that minor to be consumed under the supervision of that person.

The Liquor Act also outlaws the supply of liquor in lieu of remuneration, or having the cost of liquor deducted from remuneration. In order to obtain a licence to manufacture or distribute alcohol, applicants must have subscribed to an industry code of conduct, and consideration will be given to the applicants' contributions to combating alcohol abuse. It was anticipated that most provinces would liberalise restrictions on the sale of alcohol with a view to drawing formally unregulated suppliers into the regulated sector, while acting on public health concerns – for example, restricting sale to minors (Parry, 2005b).

The National Liquor Policy Council (NLPC), comprising the Minister of Trade and Industry and relevant Members of the Executive Councils of the provinces, formulates and

coordinates policies and cooperative governance. The council was established by provisions of the Liquor Act, and is responsible for consulting on any matters concerning the management of the liquor industry, facilitating and promoting intergovernmental relations pertaining to the liquor industry, and managing intergovernmental disputes concerning the industry (Department of Trade and Industry, 2004).

Crucial prevention policies have been developed by sectors other than health, education, social development and criminal justice. For example, the National Treasury has, over recent years, increased its excise taxes on beer, wine and spirits (Parry, 2005b; Parry, Myers & Thiede, 2003). The Department of Transport has also decreased the permissible alcohol levels from 0.08g/100ml to 0.05g/100ml, although enforcement remains an ongoing problem.

In October 2006, Cabinet approved the revised National Drug Master Plan and programme (Department of Social Development, 2006). The plan is in line with the Drug Dependency Act of 1992, which requires the government to review such a plan every five years.

The most recently reformed legislation pertaining to substance abuse is the Prevention of and Treatment for Substance Abuse Act (2008). The Act provides for the coordination of substance abuse prevention and treatment through the registration and establishment of all programmes and services; creation of conditions and procedures for admission of persons in treatment centres; establishment of a Central Drug Authority; and promotion of a collaborative approach among government departments and other stakeholders. The Act repealed the Prevention and Treatment of Drug Dependency Act (1992, as amended in 1999).

Assessing current policies: aims, scope and stakeholders consulted

Currently there are six policies and laws in place which provide the policy framework for substance abuse in South Africa:

1. Drugs and Drug Trafficking Act (1992)
2. Tobacco Product Control Act (1993)
3. National Drug Master Plan (1999)
4. National Policy on Drug Abuse Management in Schools (2002)
5. Liquor Act (2003)
6. Prevention of and Treatment for Substance Abuse Act (2008).

The aims, scope and the stakeholders consulted in the development of these policies and laws are set out in Table 19.1.

Implementing policy at local level: a municipal case study

It is beyond the scope of this chapter to assess the implementation of the policies and laws reviewed here. This information is covered in some detail in other chapters in this volume, in particular chapters on prevention (Chapter 14), gangs and shebeens (Chapter 15) and substance abuse treatment (Chapter 18).

Nevertheless, it is useful, for the purpose of this discussion, to consider the extent to which national policies and legislation can be translated into local municipal strategies. One case study is the City of Cape Town, which has developed a draft Operational Alcohol and Drug Strategy (2007–2010) (Department of Health, 2007).

This strategy aims to:

- Reduce the burden of alcohol and other drug use on the city of Cape Town and its residents, business and visitors through the provision of targeted supply and demand reduction interventions
- Define the role of the city and direct alcohol- and other drug-related (AOD) programmes and policies in the city, as well as ensure that these correspond with and contribute to provincial and national policies and plans
- Encourage interaction between health, law enforcement and welfare for the smooth running of the strategy and to avoid duplication of services
- Improve access to information regarding AOD-related harms for the city community
- Improve reporting on local interventions and their effectiveness
- Cooperate with other spheres of the government for enhanced responses to AOD.

The strategy embraces certain key principles:

- The city will work with a range of stakeholders, including other spheres of government, service providers and AOD users and those affected by their use
- The burden of AOD problems should be shared by the whole community; integrated responses are therefore required to complement provincial and national programmes and established health, social welfare and other regulatory structures, and to improve reporting to the citizens, target communities, service providers and various governmental spheres
- An emphasis will be based on evidence-based interventions
- The principle of social inclusiveness will be reflected through a commitment to reduce the impact of AOD use on our most vulnerable populations, previously disadvantaged communities, young people, people affected with HIV/AIDS, homeless people, women, elderly, mentally ill and physically disabled people
- A long-term commitment to funding and resource allocation is essential to tackle AOD-related harms
- Demand reduction is a key principle, to target prevention of new AOD use/misuse, and treatment of existing AOD problems
- A multi-prolonged approach will be adopted, to intervene in AOD-related problems and to engage simultaneously at many stages in the cycle, including prevention, early intervention, treatment and reintegration.

Substance abuse policy: current challenges

Much has been achieved in the development of substance abuse policy since the advent of the democratic era in South Africa in 1994. There is now a wide array of policy and legislative instruments in place, and an intersectoral coordinating body in the form of the Central Drug Authority. A major current challenge appears to be less in policy development, and more

in the implementation of current policy and legislation, particularly at provincial and local level. Within this broad area, there are a number of key implementation challenges:

1. **Intersectoral collaboration**: there remains an ongoing challenge of coordinating the various elements of the NDMP in a seamless fashion: for example, cooperation between the departments of Health and Social Development in the delivery of mental health and substance abuse treatment services. Within this point, an important concern is the extent to which specific sectors perceive themselves as accountable to the NDMP and the CDA, or are more inclined to follow the lead of their departmental heads, a form of 'silo' thinking that limits possibilities for collaboration.
2. **Monitoring**: there is an urgent need to develop a set of nationally agreed indicators for monitoring and evaluating all aspects, from prevention to treatment and rehabilitation. An important recent development is the Service Quality Measures Project, led by the Medical Research Council, with participation from the departments of Health and Social Development, SANCA and other service providers and research institutions. The study aims to develop a set of indicators for routine service administration and modular surveys in substance abuse treatment centres throughout the country (Fakier et al, 2009).
3. **Targets**: related to indicators, there is an urgent need for a set of nationally agreed norms and standards. The Department of Social Development is currently busy with these in relation to treatment centres, but similar targets are required for other aspects.
4. **Regulation**: given the wide array of service providers for substance abuse treatment, it is essential to create the right mix of positive incentives and regulatory muscle to improve the quality of care and the accessibility and availability of services.
5. **Enforcement**: for many sectors, the success of policies is entirely contingent on the extent to which they are enforced. A good example is the permissible alcohol level for drivers, which is stipulated by the Department of Transport, but requires active enforcement by traffic police. Unless traffic police are well trained, and provided with incentives to enforce these provisions, implementation of the policy will remain fragmented, and alcohol-related road injuries will remain high.

Notwithstanding the importance of implementation, there is also a need for policy development in relation to alcohol. Much of the current policy and legislation focuses on drugs rather than alcohol. This is despite the clear evidence of the enormous public health risk associated with alcohol abuse, as described in other chapters in this volume. In a review of the international evidence for policy-relevant strategies to address the burden of alcohol use, Parry identifies 10 key strategies (Parry, 2005a):

1. Changing the minimum legal purchase age
2. Instituting a government monopoly on retail sales
3. Instituting restrictions on hours or days of sale
4. Instituting restrictions on outlet density
5. Increasing excise taxes on alcohol
6. Sobriety checkpoints and random breath testing for motorists
7. Lowering blood alcohol concentration (BAC) limits
8. Administrative licence suspension

9. Graduated licensing for novice drivers
10. Brief interventions for hazardous drinkers.

Of these, only four have been adopted in current policy and legislation, and there remain ongoing challenges with implementation in all strategies adopted. Some strategies, such as a government monopoly on retail sales, may not be feasible within the South African context, as Parry concedes. Nevertheless, there is a need to thoroughly review current policy and legislation pertaining to alcohol, and to examine the extent to which evidence-based interventions from international experience can be adopted and enforced in South Africa.

Finally, there is a crucial need for policy evaluation research in substance abuse in South Africa. While excellent studies have been conducted of treatment service provision, and epidemiological surveillance data are available (for example, through SACENDU), there is a dearth of studies on the extent to which current policy and legislation is being implemented in South Africa. This is fertile ground that could inform future policy and legislative directions, and is crucial to ongoing attempts to combat substance abuse in this country.

Conclusion

There are certain processes that are essential for the successful development and implementation of future substance abuse policy in South Africa. These include the use of evidence, consultation with key stakeholders, a realistic vision, coordination of the various stakeholders, and implementation through concrete plans, programmes and budgets, with sufficient infrastructure and appropriate monitoring of services.

South Africa has a history of relatively fragmented substance abuse policy and legislation, but this has been consolidated to a large extent since 1999 with the National Drug Master Plan and the subsequent establishment of the Central Drug Authority.

Major current challenges include the strengthening of policy on alcohol, and the implementation of current policies and laws through intersectoral collaboration, specific sectoral planning and budget allocation, strengthening the regulatory environment and improved monitoring and evaluation.

References

Department of Health (2007), *Draft Operational Alcohol and Drug Strategy (2007–2010)*. Cape Town: Department of Health, City of Cape Town.

Department of Social Development (2006). *National Drug Master Plan 2006–2011* Pretoria: Department of Social Development.

Department of Trade and Industry (2004). National Liquor Act 59 of 2003. Available from: http://www.dti.gov.za/business_regulation/nla_act.jsp; accessed 15 August 2011.

Department of Welfare (1999). *National Drug Master Plan*. Pretoria: Department of Welfare.

Fakier, N., Kader, R., Myers, B. & Parry, C. (2009). *Measuring the Quality of Substance Abuse Treatment Services: The Service Quality Measures (SQM) Project*. Cape Town: Medical Research Council.

Flisher, A.J., Lund, C., Funk, M., Banda, M., Bhana, A., Doku, V., Drew, N., Kigozi, F.N., Knapp, M., Omar, M., Petersen, I. & Green, A. (2007). Mental health policy development and implementation in four African countries. *Journal of Health Psychology*, 12(3):505–16.

Haines, A. & Victoria, C. (2004). Evidence-based action needed on health systems. *Lancet*, 364(9441):1204.

Kilpatrick, D.G. (2010). *Definitions of Public Policy and the Law.* Charleston: National Violence against Women Prevention Center, Medical University of South Carolina. Available from: http://www.musc.edu/vawprevention/policy/definition.shtml/; accessed 15 August 2011.

Kingdon, J. (1984). *Agendas, Alternatives and Public Policies*. Boston & Toronto: Little, Brown and Company.

Myers, B., Louw, J. & Fakier, N. (2007). Alcohol and drug abuse: removing structural barriers to treatment for historically disadvantaged communities in Cape Town. *International Journal of Social Welfare*, 17:156–65.

Parry, C.D.H. (2005a). A review of policy-relevant strategies and interventions to address the burden of alcohol on individuals and society in South Africa. *South African Psychiatry Review*, 8:20–24.

Parry, C.D.H. (2005b). South Africa: alcohol today. *Addiction*, 100:426–29.

Parry, C.D.H., Bhana, A., Plüddemann, A., Myers, B., Siegfried, N., Morojele, N.K., Flisher, A.J. & Kozel, N.J. (2002). The South African Community Epidemiology Network on Drug Use (SACENDU): description, findings (1997–99) and policy implications. *Addiction*, 97:969–76.

Parry, C.D.H., Myers, B. & Thiede, M. (2003). The case for an increased tax on alcohol in South Africa. *South African Journal of Economics*, 71(2):265–81.

Roman, C.G., Ahn-Redding, H. & Simon, R.J. (2005). *Illicit Drug Policies, Trafficking and Use the World Over*. Plymouth, UK: Lexington Books.

Shiffman, J. (2007). Generating political priority for maternal mortality reduction in 5 developing countries. *American Journal of Public Health*, 97(5):796–803.

Walt, G. & Gilson, L. (1994). Reforming the health sector in developing countries: the central role of policy analysis. *Health Policy and Planning*, 9(4):353–70.

Index

Note: page numbers in *italics* refer to tables and figures.