April 2014

National Guidelines for Medication-Assisted Treatment of Opioid Dependence

National Guidelines for Medication-Assisted Treatment of Opioid Dependence

Print ISBN: 978-1-74241-944-2
Online ISBN: 978-1-74241-945-9
Publications approval number: 10253

Copyright Statements

Designed by Graphic Language Design www.gldesign.com.au

National Guidelines for
Medication-Assisted Treatment
of Opioid Dependence

Authors

Linda Gowing
Drug & Alcohol Services South Australia and
Discipline of Pharmacology, the University of Adelaide

Robert Ali
Drug & Alcohol Services South Australia and
Discipline of Pharmacology, the University of Adelaide

Adrian Dunlop
Drug and Alcohol Services for Newcastle,
New South Wales Health

Mike Farrell
National Drug & Alcohol Research Centre,
the University of New South Wale

Nick Lintzeris
Drug and Alcohol Services for South Eastern
Sydney Area Health Service

Contents

Contents

Contents

Contents

Contents

Contents

Contents

Contents

Contents

Acknowledgements

The authors acknowledge input from the Commonwealth Department of Health and a consultative group comprising Michael Aufgang (RACGP), Sue Ballantyne (Queensland Health), Denis Leahy (Pharmacy Guild), Laura Santana (AIVL), Sam Liebelt (AIVL), Anna Keoto (NSW Health), Annie Madden (AIVL), Michael McDonough (Health Victoria), Natasha Perry (Hunter-New England Health), Nghi Phung (Australasian Chapter of Addiction Medicine), Angelo Pricolo (Pharmacy Guild), Allan Quigley (Health WA), Adrian Reynolds (Tasmania Health).

This document updates and replaces four previously separate documents:

- National Pharmacotherapy Policy for People Dependent on Opioids;
- Clinical guidelines and procedures for the use of methadone in the maintenance treatment of opioid dependence;
- National clinical guidelines and procedures for the use of buprenorphine in the maintenance treatment of opioid dependence; and
- Clinical Guidelines and Procedures for the Use of Naltrexone in the Management of Opioid Dependence.

These documents have informed the development of this version; the indirect contribution of the authors of these earlier documents is acknowledged.

The work to develop these guidelines was commissioned by the Intergovernmental Committee on Drugs (IGCD) through the National Drug Strategy Cost Shared Funding Model.

Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and patient's preference in each individual case. The guideline is designed to provide information to assist decision-making and is based on the best available evidence at the time of development of this publication.

Please Note: Tasmania endorses the overall thrust of the guidelines as an important and much needed national guide for clinicians to use in treating opioid dependence, but does not endorse the framework or criteria for takeaways and unsupervised dosing.

All links to websites and phone numbers included in this document were current at the time text was finalised.

The authors have previously received funding from Reckitt Benckiser in the form of untied educational grants. Reckitt Benckiser had no role in the preparation of this document.

Foreword

This document marks a substantial step forward in the evolution of treatment for opioid dependence in Australia. It consolidates four, previously separate, documents into one, and reflects accrued experience with buprenorphine. More importantly, it seeks to make the guidelines more clearly evidence-based and useful for service providers, policy makers and consumers. The term “medication-assisted treatment of opioid dependence” that has been used in the title is a more encompassing term than “pharmacotherapy” and is increasingly being used to refer to the different treatment approaches that combine medication and psychosocial support for people who are opioid dependent.

Providing a broad policy context and framework with a view to promoting a national standard whilst recognising jurisdictional responsibilities and the need for flexibility to accommodate different jurisdictional approaches is a complex task. The efforts of all involved in providing and drawing together diverse viewpoints and expertise to produce this document are greatly appreciated. I hope the end result is practical, useful and informative.

Chair

AUSTRALIAN HEALTH
MINISTERS’ ADVISORY COUNCIL

Introduction

Opioid use in Australia

Less than 1% of the Australian population aged 14 years and over will have used heroin or another opioid for non-medical purposes in the last year[1]. Despite the low prevalence of use, the economic and social cost of opioid drug use is relatively high due to:

- loss of life through fatal overdose, with deaths related to heroin and other opioids occurring at a much younger age than deaths attributed to alcohol or tobacco;
- treatment of overdose and other medical consequences of injecting drug use;
- transmission of hepatitis C, hepatitis B and HIV;
- community loss due to criminal activity;
- law enforcement and judicial costs; and
- loss of quality of life for users and their families, including personal and economic cost of imprisonment.

Heroin, and opioid dependence in general, is a major area of focus for drug and alcohol treatment services because the harms are disproportionate to the prevalence of use.

Nature of opioid dependence

The key feature of dependence is a loss of control over use, which is seen as continued use despite drug-related legal, interpersonal and health problems as well as drug use taking priority over other activities and obligations.

LINK
Appendix 1: Definitions of opioid dependence

The reasons why people start taking alcohol and other drugs are diverse. Initial and ongoing use is influenced by a range of risk and protective factors that are biological, sociological and psychological in nature.

Risk factors	Protective factors
Individual personality	Self-control
Parental attitudes	Parental monitoring and support
Chaotic home environment	Positive social environment
Drug availability and effects	Positive relationships
Social environment	Academic competence

Not all people who use drugs become dependent. As with any other medical condition, individual vulnerability to dependence is determined by the mix of risk and protective factors, but with repeated drug use biological factors become important. It is estimated that genetic factors account for between 40 and 60 percent of a person's vulnerability to addiction, including the effects of environment on gene expression and function[2].

[1] Australian Institute of Health and Welfare 2011. *2010 National Drug Strategy Household Survey report*. Drug statistics series no 25. Cat. No. PHE 145. Canberra: AIHW. www.aihw.gov.au. Accessed 4 April 2012.

[2] *Drugs, brains and behaviour. The science of addiction*. National Institute on Drug Abuse, US Department of Health and Human Services, August 2010. Available from www.drugabuse.gov. Accessed 15/5/2013.

Introduction

The age of first use, route of administration and individual response to drug user are all factors that influence the likelihood of initial drug use progressing through regular use to dependence. Continued use leads to physiological and neurobiological changes that in turn lead to physical dependence manifested as withdrawal on cessation of use, and ongoing craving predisposing to resumption of drug use (Koob & Volkow, 2010).

Dependent drug users tend to show greater impulsiveness; make choices based on immediate benefit, with little regard to long term negative consequences; and show poor impulse control, arising from a lack of activity in the area of the brain responsible for "executive function". Factors that affect the "executive" area of brain function (such as planning, problem-solving and interpreting risk) include:

- characteristics of the person (genetics, early experiences)
- stage of brain maturation (this is one of the last areas of the brain to complete development, at around 25 years of age; consequently adolescents are more vulnerable to the development of problematic drug use) and
- brain damage, due to injury or neurotoxicity of drug use.

Drugs are thought to act through systems in the brain that have their origin in responses to stimuli that are relevant to preservation of the species (food, sex, fight and flight behaviour). In drug addiction, drug-seeking becomes the focus at the expense of natural rewards. The continual activation of the structures in the brain by drug use causes changes in neuronal systems that "hard-wire" the memory of drug use as a source of "reward" and necessary for survival. It is this in-built memory that makes addicts vulnerable to long-term relapse (meaning a return to problematic drug use) and is the basis of the chronic relapsing nature of drug dependence (Koob & Volkow, 2010).

Treatment approaches to opioid dependence

The chronic relapsing nature of drug dependence has resulted in addiction being compared with other chronic, relapsing medical conditions such as asthma, hypertension and diabetes. The similarities of these conditions are striking:

- genetic, personal choice and environmental factors play comparable roles in the aetiology and course for all these conditions;
- rates of relapse and adherence to medication are similar;
- there is no reliable cure, however compliance with treatment is associated with more favourable outcomes;
- people who are older, employed, with stable families and long-term relationships are more likely to comply with treatment and have positive treatment outcomes than those who are younger, unemployed and with less stable family support; and
- best outcomes are achieved with treatment that combines medication and behavioural interventions.

To become drug free, dependent users have to overcome the compulsion of drug use, ongoing cravings and the physical adaptation to chronic drug use. They also have to deal with psychological and social issues that may comprise both the underlying reasons

Introduction

for using drugs and the consequences of a drug-using lifestyle. The more severe and long-standing the dependence, the less alternative interests the person has to revert to – social exclusion is common. This social complexity means that recovery from drug dependence is likely to entail substantial physical, psychological and lifestyle readjustments – a process that typically requires a long period of time. Many people who develop addiction as a complication of opioid treatment of chronic, non-malignant pain may have a lesser degree of social exclusion, but the combination of pain and addiction can also result in complex treatment needs.

Medication assisted treatment of opioid dependence (MATOD) is a combination of medication (methadone or buprenorphine for substitution treatment, or naltrexone for relapse prevention treatment) and psychosocial support. The medications eliminate withdrawal, control or eliminate cravings or block the euphoric effect of further opioid use, while psychosocial support refers to the many ways in which the psychological health and the social environment of the opioid user can be addressed, to help improve both the quality and duration of life. Assistance can range from the simple (e.g. provision of food and shelter) to the complex (e.g. structured psychotherapy). Psychosocial support provided as a component of MATOD should be phased and layered to reflect changing patient needs over time, with the style and content adapted to fit preparedness for change and cognitive capacity[3].

Medications used in MATOD are of two broad types: opioid agonists and antagonists.

- Methadone, morphine, heroin, oxycodone and hydromorphone are all full opioid agonists. These drugs bind to and activate mu opioid receptors in the brain. Increasing doses of full agonists produce increasing effects.
- Naltrexone and naloxone are examples of opioid antagonists. These drugs also bind to mu opioid receptors in the brain, but do not activate them. In binding to the receptors antagonists prevent the receptors from being activated by agonists. Hence antagonists are blocking agents.
- Buprenorphine is a partial mu opioid agonist. It binds to the mu opioid receptors in the brain and activates them, but not to the same degree as full agonists. The consequence of this is that there is a ceiling effect, with the effect of buprenorphine reaching a maximum level that is not increased further even with increasing doses of buprenorphine. Like antagonists, partial agonists occupy receptors and prevent further activation by a full agonist.

LINK

See glossary for definition of agonist

See glossary for definition of antagonist

The pharmacological properties of methadone and buprenorphine are such that they can be substituted for problematic opioid drugs, referred to as opioid substitution treatment (OST). As a blocking agent naltrexone is used in abstinence-oriented programs to support relapse prevention. Inherent in these guidelines is the concept that, for people who are opioid dependent, abstinence is not easily achieved or maintained. While

[3] National Treatment Agency for Substance Misuse (2012). *Medications in recovery: Reorientating drug dependence treatment*. Available from www.nta.nhs.uk/uploads/medications-in-recovery-main-report3.pdf, Accessed 3 April 2013.

medication alone can bring about some behavioural change (Schwartz, Kelly, O'Grady, Gandhi, & Jaffe, 2012; Yancovitz et al., 1991), psychosocial support is seen as critical to sustainable change. Hence the definition of MATOD incorporates psychosocial support as an inherent component. Recovery from addiction involves multiple pathways and processes that are unique in timing and characteristics for every individual (Walter Ling, Farabee, Liepa, & Wu, 2012). Treatment of opioid dependence involves building on gains and enhancing the resolve and commitment for behaviour change, which may also be referred to as "recovery capital" as is appropriate for each individual. This typically involves monitoring progress in treatment over time and establishing multiple, achievable milestones to map a treatment pathway. In the course of a treatment pathway, goals are likely to change making ongoing goal-setting essential. At different points on the pathway, emphasis may be on quality of life, and reduction of problematic risk behaviours. Abstinence from drug use may arise from behavioural change, but will not necessarily be a goal throughout the treatment pathway.

LINK

1.2.2 Patient perspective: the treatment journey

Glossary of terms and abbreviations

Structure of treatment in Australia

Optimising the benefits of MATOD requires a balance between access and quality. Making a drug widely available improves access, but may compromise the quality and safety of treatment. Restricting a drug to being used only in specialist settings limits its usefulness as an intervention. In general, the balance between accessibility and quality is best maintained when general practitioners are trained to prescribe pharmacotherapies, and are able to refer patients or to consult with specialist drug and alcohol services.

Jurisdictions vary in their requirements for treatment services. Access will be optimal where the model of service delivery involves general practitioners and other health service providers, supported by specialist drug and alcohol services, with jurisdictional monitoring and regulation.

Pharmacological treatment of opioid dependence should be accessible to all those in need, including those in prison and other closed settings (WHO, 2009). The principles of MATOD outlined by this document largely apply to both correctional and community settings but there are a range of constraints that impact on the implementation of MATOD for people in prison and in the criminal justice system. The link between community and correctional services systems is particularly important, and it is this aspect that is given attention in this document.

Integration of opioid dependence treatment into primary care is one way to increase accessibility, although it may not be possible in all settings. Primary care practitioners will usually need support from the specialist system, through mentoring, training, consultation and referral. Treatment in primary care has the advantage of integrating addiction medical and psychiatric services into mainstream services, reducing the stigma of addiction and the professional isolation of medical staff. Integration also reduces some of the problems that clinics can develop when large numbers of patients on opioid agonist maintenance are aggregated (WHO, 2009).

Introduction

Provision of opioid substitution treatment in a specialist clinic setting enables a range of services to be brought together and provides the means of specialist support to primary health care settings. Treatment may also be collaborative with prescribing and counselling in specialist clinics, and dispensing of medication in community settings.

Clinical governance and the role of guidelines

Clinical care should be informed by and consistent with evidence based treatment guidelines. These guidelines seek to adopt a framework appropriate to support quality use of medicines. In such a framework a quality of care approach would include:

- a focus on therapeutic engagement;
- a comprehensive assessment and the development of a treatment plan;
- the provision of information to patients, including information about treatment options;
- the obtaining of informed consent;
- mechanisms for ensuring patients' confidentiality with formal written consent should information need to be shared or forwarded;
- grievance procedures;
- professional development and effective mentoring and clinical support for providers;
- regular monitoring and evaluation of patients' progress and of treatment services; and
- the opportunity for partners, family and carers to participate, within the bounds of patient confidentiality.

Policies on the objectives, indications, settings, dosage schemes and treatment regulations should be developed and clearly communicated to patients and staff.

It should be noted that this document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and patient's preference in each individual case. The aim of the document is to provide information to assist decision-making by generalist service providers. It is based on the best available evidence at the time of development.

In addition to this document, practitioners should consult with jurisdictional authorities regarding requirements for safe and effective delivery of this type of treatment, which may provide additional guidance on issues such as record keeping, approvals to prescribe, amongst other issues. Such issues are discussed in general terms in section A10 but this document is unable to reflect the variability in jurisdictional regulations.

LINK

Appendix 11: Further reading and resources

A10 Jurisdictional issues

About this document

Scope

This document is intended to provide a broad policy context and a framework for medication-assisted treatment of opioid dependence. It seeks to establish national consistency in approach, whilst acknowledging jurisdictional responsibility for health care and legislative requirements relating to controlled substances.

Where appropriate, mention is made of various medications that have been or are currently being considered for treatment of opioid dependence, but the primary focus is on those medications that are currently available in Australia and approved for use in the treatment of opioid dependence (methadone, buprenorphine, oral naltrexone). Although substantial trials of prescribed heroin (heroin-assisted treatment) have been undertaken overseas (Ferri, Davoli, & Perucci, 2011) and the approach adopted by some countries as a treatment option, this option is not currently available in Australia. Other medications such as slow release oral morphine (Bond, Reed, Beavan, & Strang, 2012), dihydrocodeine (Robertson et al., 2006) and depot and implant preparations of naltrexone are the subject of ongoing research but are not currently registered for therapeutic use in Australia. These approaches are not discussed in this document.

Another opioid antagonist, naloxone (Narcan®) is widely used in Australia in the treatment of opioid overdose. In several countries naloxone is being distributed to opioid users and their families to support the effective management of overdose and reduction of deaths due to opioid overdose (Baca & Grant, 2005). In some jurisdictions in Australia, programs to promote naloxone prescribing for the prevention of overdose deaths have been, or are being developed. This application of an opioid antagonist in people who are opioid dependent does not meet the definition of medication-assisted treatment used in this document, and hence this use of naloxone is not covered in any detail.

This document provides clinical guidelines on approaches involving the use of methadone, buprenorphine or naltrexone for the treatment of opioid dependence. It aims to provide guidance in the selection and management of patients seeking pharmacotherapies for opioid dependence, and to support the provision to patients of accurate information about methadone, buprenorphine and naltrexone.

These guidelines are intended in particular for generalist settings, i.e. general practice and hospital, clinic or community settings not specialised in the treatment of alcohol and other drug problems. This includes acute care settings where some practitioners (e.g. anaesthetists) may have specialist skills in the pharmacology of opioid drugs, but not the treatment of addiction. As such, the guidelines identify situations where it is considered appropriate for advice to be sought from practitioners with specialist experience of the treatment of problematic alcohol and other drug use, or to refer patients to such specialists. Clinicians working in specialist drug and alcohol services may also derive some benefit from this document, but the primary audience is non-specialist.

About this document

Structure

This document can be printed to provide a hard-copy reference, but incorporates links to facilitate electronic use.

There are two main parts to the document:

- Part A presents the guidelines as concise recommendations, with a grading indicating the strength or weight and basis of each statement, and with links to other relevant sections of the document, or external documents; and
- Part B provides supporting information.

Process for development of guidelines

This document is informed by national and international research literature, previously published guidelines and clinical and consumer experience in Australia with the pharmacotherapies covered by the guidelines.

The first stage involved the development of a list of issues to be addressed in the guidelines, based on previous guidelines and the experience of the authors. This list of issues was discussed and refined by a consultative group comprising State and Territory representatives with experience of pharmacotherapies for opioid dependence, and representatives of the Royal Australian College of General Practitioners (RACGP), the Chapter of Addiction Medicine (Royal Australasian College of Physicians), the Pharmacy Guild, and the Australian Injecting and Illicit Drug Users League (AIVL). Comments were also provided by the Commonwealth Department of Health.

Literature searches were undertaken looking for recent (published since 2000) systematic reviews and clinical trials of pharmacotherapies used for the treatment of opioid dependence. Evidence statements were developed for the issues listed, following the process recommended by the National Health and Medical Research Council[4].

Specific wording of the guidelines and supporting information were collated, and a grading was allocated to the guidelines based on the evidence statements.

The resultant document was circulated to the consultative group, the Commonwealth Department of Health and the Intergovernmental Committee on Drugs for comment before being finalised for publication.

[4] *NHMRC levels of evidence and grades for recommendations for developers of guidelines*, December 2009; www.nhmrc.gov.au, accessed 21 February 2012

About this document

Grading of guidelines

Recommendations supported by research evidence are graded according to NHMRC definitions[5] (with a 4-star rating system rather than letters):

Grade of recommendation	Description
★★★★	Body of evidence can be trusted to guide practice
★★★	Body of evidence can be trusted to guide practice in most situations
★★	Body of evidence provides some support for recommendation(s) but care should be taken in its application
★	Body of evidence is weak and recommendation must be applied with caution

Recommendations based on a consensus of clinical experience are indicated by **|C|**, recommendations reflecting a standard of care that should be routine in competent clinical practice are indicated by **|S|**, and those established by regulatory requirements by **|R|**.

✦ is used to indicate areas where caution is required and specialist advice or referral is recommended.

Terminology

These guidelines use the term “patient” rather than “client”. The primary audience for the document is medical practitioners who generally use this terminology.

Varying terminology has been used for approaches involving the prescription of opioid medications for the treatment of opioid dependence, including “methadone maintenance”, “heroin assisted treatment”, “opioid substitution treatment”, etc. In these guidelines the terms “medication-assisted treatment” and “opioid substitution treatment” are used. “Medication-assisted treatment” is becoming widely used internationally as indicating the use of medication and psychosocial support in combination and is appropriate for these document given its wide scope. “Opioid substitution treatment” refers to medication-assisted treatment using opioid agonists (methadone, buprenorphine).

[5] *NHMRC levels of evidence and grades for recommendations for developers of guidelines*, December 2009; www.nhmrc.gov.au, accessed 21 February 2012

PART A

Guidelines for Medication-Assisted Treatment of Opioid Dependence

Recommendations in these guidelines are rated

★ One to four stars indicates the strength of the supporting evidence.

|C| If evidence is based on a consensus of clinical experience

|S| Indicates a standard of care that should be routine in competent clinical practice.

|R| Indicates a regulatory requirement.

✦ Red flag indicates areas where caution is required and specialist advice or referral is recommended.

See page 8 for a detailed explanation.

Assessment

Initial assessment of a person using opioid drugs should follow standard practice for assessment of a complex clinical condition and incorporate collateral information where appropriate |S|. Collateral information might be obtained from other health care providers, family members, partners and carers as well as regulatory and prescription monitoring systems, according to usual standards of privacy and confidentiality.

LINK
3.1 Assessment and treatment engagement
A8 Consumer information and perspective

Assessment should be linked to the practitioner's skills, experience and available resources |S|. Complex issues (e.g. high risk behaviours, significant misuse of other drugs, doctor shopping, serious comorbid physical or mental health conditions) make specialist addiction medicine advice or referral advisable. Such issues are indicated in these guidelines with this icon ✦.

A comprehensive biopsychosocial assessment and case formulation provides the basis for treatment planning, indicates additional service needs and the type of treatment likely to be appropriate |S|. Assessment should cover the broad range of medical, physical and mental health conditions that frequently accompany opioid dependence |S|.

A1.1 Reason for treatment

Individuals come to the attention of treatment providers for a range of reasons, including those seeking treatment for their substance use, or for other health or social problems (that may or may not be drug-related). The reason for presentation will impact upon the immediate treatment goals and the type of treatment that may be acceptable and appropriate for the patient |S|.

LINK
1.2.2 Patient perspective: treatment journey
1.2.4 Types of treatment

A1.2 Assessing substance use and previous treatment

A1.2.1 History

A comprehensive substance use history is essential, and involves assessment of all types of drugs used (including illicit and pharmaceutical opioids, alcohol, cannabis, stimulants, benzodiazepines), duration of use, quantity and frequency of recent use, route of administration, and time of last use |C|.

Assess previous drug treatment episodes attempted by the patient, including their perspective on what has worked before, the factors leading to relapse, and what treatment the patient is prepared to consider at this time.

A1.2.2 Physical and mental state examination

General physical and mental state examination should be conducted based upon the medical history and presenting circumstances.

Assess for intoxication and withdrawal (taking account of reported last drug use) |S|:

- withdrawal severity is an indication of likely severity of dependence, and may serve as a pointer to the timing and amount of first dose of medication (recent use of opioids increases the likelihood of withdrawal being precipitated by buprenorphine or naltrexone);

LINK
Precipitated withdrawal in 2.1.2

A1 Assessment

- intoxication with central nervous system depressants such as benzodiazepines and alcohol increases the risk for overdose in combination with methadone or buprenorphine;

LINK

Appendix 6: Signs of intoxication

Appendix 5: Withdrawal states

Appendix 2: Assessment of opioid withdrawal

SIGNS AND SYMPTOMS OF OPIOID WITHDRAWAL	
Dilation of pupils	Lacrimation
Anxiety	Rhinorrhoea
Muscle and bone ache	Abdominal cramps
Muscle cramps	Nausea
Sleep disturbance	Vomiting
Sweating	Diarrhoea
Hot and cold flushes	Palpitations
Piloerection	Rapid pulse
Yawning	Raised blood pressure

SIGNS OF OPIOID INTOXICATION	SIGNS OF OPIOID OVERDOSE
Constriction of pupils	Pinpoint pupils
Itching and scratching	Loss of consciousness
Sedation and somnolence	Respiratory depression
Lowered blood pressure	Hypotension
Slowed pulse	Bradycardia
Hypoventilation	Pulmonary oedema

Examine peripheral sites for evidence of previous injections |C|, documenting any related complications (e.g. infections). Injecting into the groin or neck are indications of high risk drug use which may benefit from specialist advice or referral |C|. ✦

LINK

2.6.8 Infections in injecting drug users

A1.2.3 Investigations

Urine drug screening is useful to corroborate patient history and establish recent opioid and other substance use. However delays in obtaining results should not delay treatment initiation where the diagnosis can be clearly established |C|. Clinicians should be aware of the potential for an adversarial relationship with the patient if the purpose of urine drug screening is poorly communicated |C|.

LINK

Urine drug screening in A4.3.2

Investigations for other conditions, either related to the presenting condition or that are related to the patient's drug use (e.g. blood borne viruses, liver disease) should also be undertaken as needed, although these are often better delayed until stabilisation has been achieved.

A1.2.4 Diagnosing substance use disorders

Establishing a diagnosis of opioid dependence is a requirement for opioid substitution treatment |R|. The International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM) provide widely accepted definitions of dependence.

LINK

Appendix 1: Definitions of opioid dependence

A1 Assessment

Dependence on pharmaceutical opioids in the context of chronic pain can pose a diagnostic dilemma. Chronic use of high doses of opioids, such as morphine, oxycodone or codeine, will result in neuroadaptation (tolerance, withdrawal) in most patients, but this is not necessarily sufficient for a diagnosis of opioid dependence. Features consistent with diminished control over opioid use (e.g. multiple dose escalations, unsanctioned routes of administration, use for reasons other than pain, difficulties in reducing opioid use) should be explored. Consultation or referral to an addiction or pain medicine specialist may be advisable.

LINK

A2.1.4 Chronic pain syndromes and pharmaceutical opioid dependence

2.6.10 Management of pain

A1.3 Assessment of other health and social issues

Co-existing health and psychosocial conditions are likely to influence the preferred treatment approach, setting and broad (holistic) treatment plan, including the need for specialist advice or referral |S|.

The clinician should assess general health and well-being, targeted within the context of the patient's substance use. Opioid and other substance use is commonly associated with a range of:

- physical conditions (e.g. chronic non-malignant pain, liver, cardiovascular, injecting-related infections, endocrine)
- psychiatric conditions (e.g. anxiety, depression, cognition)
- social problems (e.g. unemployment, housing, financial, relationships)
- high risk behaviours (e.g. overdose, self-harm, child protection and domestic violence).

These conditions and risk factors should be assessed for each individual which may require assessment over a period of time, and involve different health and welfare providers. As social situations are subject to change they should be revisited regularly throughout the course of care.

The timing of assessment and investigation of other health issues should be tailored to the individual patient's presentation. For example, screening for blood borne viruses (HIV, HCV, HBV) rarely needs to be conducted at the initial assessment, and may be better deferred until the patient has stabilised in treatment and is better able to engage in pre- and post-test counselling.

Treatment Planning

As in other areas of chronic disease management, addiction treatment planning should:

- be a continuous process;
- involve the patient and reflect the patient's circumstances and case complexity;
- be based on coordinated care across service providers to address multiple domains;
- be documented so as to be meaningful to the patient, their carers and other service providers |S|.

All types of available treatment for opioid dependence should be considered in consultation with the patient, taking into account the patient's circumstances and treatment preferences, and be based upon the evidence of effectiveness and safety of available options |S|.

The principles of informed consent should be observed in selecting and referring patients to treatment services |S|.

The table below lists key factors for the different treatment approaches that are relevant to selection of the type of treatment, but is not an exhaustive summary of evidence for the effectiveness of the different approaches.

TYPE OF TREATMENT	ADVANTAGES	DISADVANTAGES
Substitution treatment	• Strong evidence of capacity to – reduce opioid use ★★★★ – decrease mortality ★★★ – improve quality of life • Avoids withdrawal in people who are ill or unstable • Capacity to retain patients in treatment ★★★★ • Widespread availability	• Expense to patient (daily travel dispensing fees). • Side effects • Stigma • Restrictions of supervised dosing (lifestyle travel etc) • Prolonged withdrawal on cessation
Detoxification	• Short-term commitment • Attractive to consumer • Low threshold easy access and • Entry point to treatment	• Poor long-term outcomes if stand-alone treatment • Poor long-term outcomes if stand-alone treatment • Increased overdose risk following withdrawal (loss of tolerance) • Can lead to destabilisation of other health conditions (chronic pain, mental health)
Antagonist treatment (naltrexone)	• Effective in decreasing opioid use in highly motivated well-supported people ★★ • Opioid-free' medication	• Poor retention for most people ★★ • Limited acceptance • Side effects • Complicates pain management • Cost to patient • Requires detoxification prior to initiating naltrexone • Increased overdose risk following cessation due to loss of tolerance ★★★

LINK
A8 Consumer information and perspective

LINK
1.2.2 Patient perspective: the treatment journey
1.2.3 Importance of integration

LINK
2.3.2 Effectiveness of substitution treatment
2.2.3 Medications to manage withdrawal
2.4.1 Effectiveness of naltrexone treatment

A2 Treatment Planning

TYPE OF TREATMENT	ADVANTAGES	DISADVANTAGES
Residential	• Effective for those with complex social problems and poor living skills • 'Medication-free'	• Requires commitment of time and separation from home and community • Long-term outcomes depend on aftercare • Completion of detoxification usually a requirement for entry • Expensive to provide • Often waiting lists
Outpatient counselling (no medication)	• Some effectiveness in substance abuse problems of lesser severity and early stages	• Evidence indicates poor outcomes in more severely dependent populations • High variability in quality of counselling services

A stepped care approach to treatment delivery suggests using less restrictive treatment approaches for those with low severity dependence (e.g. detoxification, counselling), increasing to more intensive treatment options (substitution treatment, residential) for those with more severe and entrenched problems **|C|**.

Factors that indicate particular treatment directions **|C|**:

- certain medical and psychiatric conditions (e.g. chronic pain, psychotic disorders, acute medical conditions such as infective endocarditis, HIV) can be destabilised during detoxification and attempts at sustaining an opioid-free lifestyle; such patients are often better directed to opioid substitution treatment
- women who are opioid-dependent and pregnant should usually be directed to opioid substitution treatment due to the risk of antenatal complications associated with detoxification, and high rates of relapse to heroin or other opioid use with other treatment approaches;
- people with a preference for abstinence-based interventions who are well supported and well motivated are more likely to respond to counselling with or without naltrexone
- people with poor living skills and unstable social circumstances may benefit from residential treatment.

LINK
A7.1 Pregnancy and breastfeeding.
2.6.3 Pregnancy and breastfeeding

Particular patient circumstances or populations which impact upon treatment planning are discussed in more detail in the next section.

Substitution treatment has specific requirements that need to be addressed in the treatment plan, including jurisdictional approval to prescribe methadone or buprenorphine, and dispensing arrangements **|R|**.

LINK
A10.3 Authorisation, training and support of prescribers and dispensers

Once diagnosis, consent to treatment and choice of modality is established, treatment should be commenced without delay **|C|**. If there are concerns about initiating treatment safely and effectively, specialist referral is recommended. ✦

At commencement of treatment a plan should be developed, and should then be actively reviewed over the course of the treatment episode. The treatment plan should involve appropriate referral to relevant services where the selected treatment approach cannot be delivered by the assessing service.

LINK
3.3 Treatment planning

A2 Treatment Planning

A2.1 Situations that may influence treatment planning

A2.1.1 Polydrug use

Polydrug use is common amongst people who are opioid dependent. Use of alcohol, benzodiazepines or other sedatives in conjunction with opioids is of particular concern due to the increased risk of overdose, particularly during methadone induction and during withdrawal attempts. Polydrug use should be regularly assessed prior to and during treatment for opioid dependence. Referral to specialist services is indicated for patients with misuse or dependence to multiple drugs or alcohol but polydrug use should not be a reason to withhold opioid substitution treatment |C|.

LINK
A1.2 Assessing substance use and previous treatment
2.6.7 Polydrug use

A2.1.2 Acute medical conditions

Regular opioid use is associated with a range of health problems that may cause the patient to seek medical attention, and can be an opportunity to initiate opioid dependence treatment. Liver disease (viral infections and alcohol use) is particularly common and requires assessment and referral for specialist treatment as appropriate (e.g. treatment for HCV infection). Long-term anti-viral treatment for HCV and HIV appears to be more effective for injecting drug users who are engaged in opioid substitution treatment. Seek specialist advice or referral for patients with severe or acute medical problems, including hepatic, renal or respiratory failure |C|.

LINK
2.6.8 Infections in injecting drug users

A2.1.3 Psychiatric comorbidity

It is often difficult to establish whether opioid dependence is causing mood disturbance, or vice versa. Use of other substances (e.g. stimulants, alcohol) and sedative withdrawal may be associated with psychiatric problems (including psychotic, affective and cognitive) problems. In general, treatment of opioid dependence should be initiated with regular reviews of the patient's mental health. Patients with persistent and/or severe presenting psychiatric problems (including risk of harm to self or others) may require more immediate assessment and treatment of their psychiatric condition, and specialist referral should be sought |C|.

LINK
2.6.6 Comorbid mental health conditions

A2.1.4 Chronic pain syndromes and pharmaceutical opioid dependence

Over the past 10 years there has been a trend of increasing misuse of pharmaceutical opioids, including over-the-counter preparations. The boundary between chronic pain and addiction management is complex, with a continuum of presentations ranging from some people abusing pharmaceutical opioids rather than heroin, and others commencing opioid use for management of chronic pain and then progressing to opioid dependence. Whilst both methadone and buprenorphine can be used effectively in treating patients with chronic pain and opioid dependence, a comprehensive treatment plan that addresses pain management is required. Specialist advice or referral is recommended for people with chronic pain and opioid dependence because of the potential complexity of managing both conditions |C|.

LINK
2.6.10 Management of pain

A2 Treatment Planning

A2.1.5 People with a recent interruption to regular opioid use

This may occur, for example, through recent detoxification, incarceration or hospitalisation. The interruption to regular opioid use will have resulted in lowered opioid tolerance, and if substitution treatment is preferred, cautious dosing regimens should be used. Some patients may not have recently used opioid drugs, but nevertheless have a history of opioid dependence and a high risk of returning to opioid use (e.g. following release from prison). It may be appropriate to offer substitution treatment with methadone or buprenorphine even when neuroadaptation is not evident, after consultation with specialist services **|S|**.

Release from prison is a time of high overdose risk for opioid users due to a reduced tolerance to opioids developed during imprisonment. The provision of treatment during imprisonment and pre-release, the provision of advice in relation to the higher risk of overdose, and facilitation of referral to ongoing treatment in a community setting are important to improved outcomes for this group **|C|**.

LINK

A7.4 Prisoners

2.6.9 Prisoners

In general hospital patients (including mental health admissions), any ongoing treatment of problematic opioid use or dependence identified as required should be addressed through referral to addiction treatment services as part of the discharge processes. This should be accompanied by appropriate notification to the patient's general practitioner **|C|**. It is often advantageous to commence opioid substitution treatment while the person is in hospital as this may facilitate treatment of the problem that led to admission. In this case, clear arrangements for continued treatment following discharge are important **|C|**.

A2.1.6 Child protection

The population of opioid-dependent people is young relative to the general population and are likely to be parents. At the same time, people who are opioid dependent are more likely than the general population to have a history of neglect and abuse during their childhood and may experience problems as parents. This makes it important to consider issues around child protection **|R|**, and health professionals should be aware of mandatory reporting requirements. It also points to the value of facilitating the development of parenting skills as a way of breaking the cycle of abuse and neglect **|S|**.

LINK

2.6.4 Parenting and child protection issues

A8 Consumer Information and perspective

A2.1.7 Difficulties attending dosing facilities

Temporary or long-term physical disability may make attendance at a dosing facility difficult. Alternative arrangements (including the possibility of home dosing) are worth exploring as it is desirable to retain the patient in treatment **|C|**. People who are itinerant (due to work or cultural background) are likely to be unable to comply with the structure of substitution treatment and alternative treatment options should be considered.

Detoxification

This section focuses on the management of withdrawal from heroin or unsanctioned use of pharmaceutical opioids; cessation of methadone or buprenorphine at the end of a period of substitution treatment is covered in section A4.6.

LINK
A4.6 Cessation of substitution treatment

The delivery of detoxification or withdrawal services entails:

- assessment
- treatment matching
- planning for withdrawal
- supportive care and
- linkages with services for further treatment and support.

Detoxification in opioid dependence should always be considered as part of a structured treatment approach **|C|**.

A3.1 Objectives of detoxification

A realistic set of objectives for detoxification services is as follows:

1. To alleviate distress. Palliation of the discomfort of opioid withdrawal symptoms is an important reason for patients presenting for treatment, and one of the primary aims of withdrawal services.
2. To prevent severe withdrawal sequelae. Although opioid withdrawal on its own is rarely life-threatening, withdrawal can present various serious problems:

- Complication of concomitant medical or psychiatric conditions, or dehydration in an individual with poor baseline nutritional status or diabetes.
- Increased risk of overdose following withdrawal. This can occur with resumption of opioid use following the reduction in opioid tolerance that accompanies withdrawal, and due to the combined sedative effects of opioids and medications used for the management of opioid withdrawal (e.g. benzodiazepines).

3. To interrupt a pattern of heavy and regular drug use. Many patients want treatment to end their opioid use completely during the withdrawal episode, intending to stay off opioids for a set period of time afterwards. However, giving up entirely is not the goal of every patient.
4. To provide linkages to and enable engagement in ongoing treatment for their drug dependence.
5. To get help with other problems. While some people will be unwilling or unable to continue in ongoing drug treatment programs, they may benefit from contact with welfare services (e.g. accommodation), general support and case management services (e.g. outreach workers), or primary or specialist health services.

A3 Detoxification

A3.2 Settings for withdrawal

Management of withdrawal may occur in a range of settings:

- Hospitals, particularly when drug users have been admitted for other reasons;
- Residential services, which provide a safe, supportive environment for withdrawal management, but a lower level of medical care than hospitals;
- Ambulatory (outpatient and/or home-based services) for those individuals with stable social settings and without significant medical or psychiatric complications or dependence on other drugs.

Selection of setting and approach to detoxification should take into account the goal of the care episode, the purpose of detoxification and timescale **|S|**.

Intensive inpatient care is appropriate with:

- Unstable medical or psychiatric condition;
- Polydrug dependence;
- History of medical or psychiatric conditions, or uncertain past drug use indicate a need for close monitoring.

Supported residential care, such as a community withdrawal unit, is appropriate with:

- Unsupportive home environment, such as with other drug users, or without anyone reliable to supervise and support the patient;
- Repeated failure at outpatient withdrawal.

A3.3 Supportive care and monitoring

Psychosocial support during the withdrawal episode should be aimed specifically at helping the patient through problems associated with withdrawal and in facilitating post-withdrawal links.

LINK
2.2.5 Adjunct therapies in detoxification

Patients should be reviewed regularly by the treating team according to the patient's condition and treatment settings. Review should include assessment of withdrawal symptoms and severity, adverse events, other drug use and any concerns the patient might have. Structured withdrawal scales may assist with monitoring.

LINK
Appendix 2: Assessment of opioid withdrawal

A3.4 Patient information

Patients need information regarding:

- the risk of overdose should they relapse after withdrawal as well as approaches to prevent and manage overdose;
- the nature and duration of withdrawal symptoms;
- strategies for coping with symptoms and cravings;
- strategies to manage high-risk situations;
- the role of medication.

LINK
Appendix 10: Prevention and management of opioid overdose

A3 Detoxification

People undergoing withdrawal often have limited concentration and information may have to be repeated, perhaps even re-phrased, to be fully understood and absorbed. Written information is valuable in these circumstances, and is also recommended to support patients and their relatives.

A3.5 Medication approaches for withdrawal

Two distinct medication approaches are recommended for the management of opioid withdrawal:

- Abrupt cessation of opioid use and symptom amelioration using non-opioid drugs (usually benzodiazepines, non-steroidal anti-inflammatory drugs, antiemetics, clonidine, antispasmodic drugs (such as hyoscinebutylbromide) for relief of symptoms;
- Short-course (usually less than 1 month) of reducing doses of buprenorphine.

Both of these approaches are well supported by evidence, but the use of buprenorphine to manage withdrawal is associated with significantly better amelioration of withdrawal than clonidine and supplementary medications |★★★★|. It is the most flexible approach in that it supports cessation of medication with minimal rebound withdrawal symptoms while also enabling transfer to naltrexone for relapse prevention treatment, or to substitution treatment if the detoxification attempt is not successful.

LINK
2.2.3 Medications to manage withdrawal

The appropriate starting dose of buprenorphine and duration of withdrawal treatment will vary according to the clinical presentation of each individual. In general, higher doses and longer duration of treatment would be preferred in outpatient settings where the risk of unsanctioned opioid use is greater.

The first dose of buprenorphine should be administered once mild withdrawal is apparent to avoid the risk of precipitated withdrawal.

LINK
2.3.5 Induction into substitution treatment

There is research evidence for the use of reducing doses of methadone for the management of opioid withdrawal, but the duration of tapered methadone withdrawal interventions tend to be greater than a month, blurring the line between withdrawal management and substitution treatment. While research evidence directly comparing methadone and buprenorphine for the management of opioid withdrawal remains limited, the flexibility of buprenorphine provides advantages in a withdrawal context.

Detoxification can also be achieved using opioid antagonists (naltrexone and/or naloxone), also known as antagonist-induced withdrawal or rapid detoxification. This approach should only be considered as a means of facilitating induction of naltrexone to support relapse prevention treatment. Antagonist-induced withdrawal with minimal sedation is feasible, but the evidence base is weak |★★|. Specialist referral is recommended. Antagonist-induced withdrawal should only be provided in facilities that have the capacity to retain people as inpatients in the event of severe withdrawal, and only following approval by that facility's drug review committee or other formal approval mechanism. Patients should be properly informed, and consent obtained, which includes information that the use of naltrexone is an off-label indication.

LINK
Use of opioid antagonists in detoxification in 2.2.3

A3 Detoxification

Rapid detoxification causes considerable physiological stress. Contraindications to rapid detoxification include:

- pregnancy;
- a history of cardiac disease – particularly ischaemic heart disease, arrhythmia, hypertrophic cardiomyopathy – or evidence of heart disease on clinical examination;
- chronic renal impairment;
- decompensated liver disease – jaundice and/or ascites, hepatic encephalopathy;
- current dependence on benzodiazepines, alcohol or stimulants;
- history of psychosis.

Antagonist-induced withdrawal under heavy sedation or anaesthesia is not supported because of increased risk of serious adverse effects, lack of additional benefit, cost and use of scarce intensive care resources |★★★★|

LINK

Use of opioid antagonists in detoxification in 2.2.3

The abrupt cessation of chronic drug use without medication is feasible, but typically associated with high failure rates and research evidence does not support this approach. Unmedicated withdrawal is best reserved for people who are unlikely to experience severe withdrawal, in a setting with appropriate care and support, and the capacity to intervene if the level of discomfort becomes unacceptable to the patient. Control of vomiting and diarrhoea is particularly important to prevent dehydration which can have serious consequences if left untreated.

A3.6 Planning services after withdrawal

The pressures and strains of using drugs, key life events (‘turning points’) and the availability of social support are important factors impacting on the likelihood of successful withdrawal – the exact detoxification technique used is less important.

Withdrawal is associated with very high rates of relapse without structured, ongoing treatment for dependence. Suitable post-withdrawal treatment options that address opioid dependence as well as any concurrent alcohol or other drug dependence, should be considered for each client. Withdrawal services should facilitate referral and engagement to ongoing treatment.

Detoxification services should communicate with the patient’s treating medical practitioner through a discharge summary |S|.

Substitution treatment

A4.1 Choice of medication

A substantial body of research evidence supports a conclusion that both methadone and buprenorphine are safe and effective in the treatment of opioid dependence. |★★★★|. The choice between methadone or buprenorphine for opioid substitution treatment should be made in consultation with the patient, and informed by the patient's preference and goals. However, there are factors that indicate particular directions, as summarised below.

LINK
2.3.2 Effectiveness of substitution treatment

- It is easier to transition in and out of treatment with buprenorphine compared to methadone. This is both an advantage in terms of greater patient flexibility, and a disadvantage with lower rates of retention in treatment with buprenorphine |★★★|.
- Whilst both buprenorphine and methadone typically have a range of opioid-like side effects, there is considerable individual variation in the experience of side effects with different opioids. If side effects are experienced with one medication, it is worth trying the other. Some longer-term side effects (e.g. impact on sex hormones|★★|, sleep apnoea |★|, prolonged corrected QT (QTc) interval |★★|) are more common with methadone.

LINK
2.1.1 Methadone Safety and side effects
2.1.2 Buprenorphine Safety and side effects
2.3.7 Adverse effects

- Drug interactions are more likely to be clinically relevant with methadone |★★★|. In particular, interactions with medications metabolised by the CYP450 hepatic system are clinically more relevant with methadone, with either induction of methadone metabolism (reduced methadone effects), or inhibition (increased methadone effects) that require monitoring of symptoms and may require dose adjustment. This can be particularly relevant for patients taking medications for HIV or TB.

LINK
Drug interactions in 2.3.7

- Some patients report that methadone has greater impact upon cognition than buprenorphine, with stronger sedation and opioid-like subjective effects |★|. This can be a therapeutic advantage for some patients with concurrent psychological distress. In contrast, many patients describe greater 'clarity of thought' with buprenorphine – an advantage for patients requiring good cognitive function (e.g. those employed, caring for children, studying, driving, elderly patients with other conditions affecting cognition, and patients taking other sedative medications)..

LINK
A4.4.2 Driving
Driving in 2.6.11

- Methadone has greater sedating effects and is more commonly associated with overdose than buprenorphine, particularly in the context of;
  (a) the first two weeks of treatment as tolerance increases |★★★|,
  (b) in combination with other sedatives (alcohol, benzodiazepines) |★|, and
  (c) use by individuals for whom the medication was not prescribed – in particular children and other opioid-naïve individuals |★★★|. Consequently buprenorphine should be the preferred medication where there is limited opportunity for monitoring or supervision of dosing.

LINK
Overdose in 2.3.7

- Induction of substitution treatment with buprenorphine is usually safer and easier, with maintenance doses reached more quickly than is the case with methadone |★★★|. However, precipitated withdrawal can be an issue if buprenorphine is commenced too soon after the last use of a full opioid agonist, and this can be a barrier for some patients commencing and engaging in treatment |★★|.

LINK
Precipitated withdrawal in 2.1.2

A4 Substitution treatment

A4.2 Induction

The goal of the first month of treatment is to safely achieve an adequate dose of medication, stabilise the patient's opioid use, and to address co-existing conditions |C|. Other conditions that may need to be addressed early in treatment include advice on pregnancy and contraception, sexual health, child protection and domestic violence, blood-borne viruses, dental care, mental health (particularly suicide risk), sleep and nutrition, and tobacco use.

Key objectives of the induction dose regimen are:

- reduction of withdrawal symptoms;
- reduction of cravings;
- reduced unsanctioned opioid and other drug use; and
- patient satisfaction and engagement in treatment.

The differing pharmacological properties of methadone and buprenorphine mean that induction strategies are different. The greater risk of opioid toxicity and overdose during induction with methadone necessitates commencing at a low dose and a slow rate of dose increase (usually over weeks in outpatient settings). The partial agonist properties of buprenorphine result in less effect on respiratory function allowing for more rapid induction to a higher dose. Achieving an adequate dose of buprenorphine as quickly as possible (usually within three days) is associated with an improved rate of retention in treatment. The induction strategies for methadone and buprenorphine are outlined in more detail below.

A4.2.1 Methadone

Key principles:

1. Methadone is sedating and can cause overdose in too high doses, particularly in those with low opioid tolerance, and in combination with other sedatives, or in those with altered pharmacokinetics (e.g. due to hepatic failure, drug interactions).
2. The elimination half-life of methadone is typically in the range between 24 and 48 hours, but extremes either side of this range have been recorded. Methadone accumulates in the plasma during induction, with achievement of steady state equilibrium on a dose after approximately three to five half-lives (4-7 days). Patients should be told to expect increasing opioid effects after each dose during this time.
3. Methadone has a delayed onset of action – with peak effects achieved two to four hours after dosing. Patients should be cautious in using other drugs (e.g. benzodiazepines, alcohol) during initiation of methadone treatment. Patients should be assessed two to three hours after a dose to observe the peak effects of methadone (assessing for intoxication), and 24 hours after a dose to assess the extent to which methadone dose is preventing withdrawal.

LINK
2.1.1 Methadone

A4 Substitution treatment

(a) Recommended regimen for outpatients with unsanctioned use of opioids

- The opioids involved are likely to include heroin, and injected morphine, and codeine.
- All doses of methadone should be supervised, where possible, and a clinician (doctor, nurse, pharmacist) should review the patient daily during the first week of treatment, corresponding to the greatest risk period for methadone-related overdose. The review provides an opportunity to assess intoxication (e.g. sedation, constricted pupils) or withdrawal symptoms, side effects, other substance use and the patient's general well-being.
- Commence with 20 to 30mg daily. Lower doses (e.g. 20mg or less) are suited to those with low or uncertain levels of opioid dependence, with high risk polydrug use (alcohol, benzodiazepines) or with severe other medical complications. Higher doses (30-40mg) should be considered with caution if clinically indicated, at the discretion of the prescriber. Consultation with a specialist is recommended before commencing patients at doses greater than 40mg because of the risk of overdose.
- Dose increases should be made following review of the patient and should reflect side effects, features of withdrawal (suggesting not enough methadone) or intoxication (suggesting too much methadone or other drug use), ongoing cravings and substance use.
- Dose increments of 5 to 10mg every three to five days will result in most patients being on doses of between 30 and 50mg by the end of the first week, and 40 to 60mg by the end of the second week.
- Supplementary doses can be considered for patients returning in severe withdrawal 4 to 6 hours after dosing, but only after review by the prescriber. This requires coordination between the prescriber and dispenser.
- The dose should be gradually increased in order to achieve cessation (or marked reduction) in unsanctioned opioid use, and alleviation of cravings and opioid withdrawal features between doses, whilst minimising methadone side effects. Daily methadone doses above 80mg will also markedly reduce the effects of any ongoing heroin or other opioid use.

Consider specialist advice or referral in the following circumstances ✦:

- patients with an unclear level of opioid tolerance, high-risk polydrug use, concomitant physical conditions or use of other medications that may affect the metabolism of methadone;
- patients seeking higher and more rapid dose increases (inpatient settings with close monitoring may also be helpful); and
- patients who have difficulty stabilising on a dose of methadone due to continued substance use, side effects or other complications.

When deciding on induction of methadone, take account of pharmacy availability for supervision of dosing and monitoring of response. If 7 day pharmacy services are not available, the commencement of treatment should be timed so that induction is well underway before the first day of unsupervised dosing.

A4 Substitution treatment

(b) Recommended regimens for patients transferring from prescribed pharmaceutical opioid preparations

The pharmaceutical preparations involved include oxycodone, fentanyl, hydromorphone and slow release oral morphine

LINK
2.6.10 Management of pain

Key principles:

1. Do not assume that what is being prescribed is what is being taken – patients may be using more or less than what is prescribed.
2. Published equivalent opioid doses are not reliable for guiding dose transfers onto methadone |C|, as they usually relate to short-term, not chronic opioid use, describe analgesic equivalence for single doses and not 24-hour dosing periods, and have usually been determined with relatively low levels of opioid use (e.g. comparing 20 or 30mg morphine). Multiple factors impact on dose conversion and specialist advice should usually be sought |C|. ✦

LINK
Appendix 8: Equivalent opioid doses

The approach to transferring from prescribed opioids (e.g. sustained-release oral morphine, oxycodone) to methadone is often determined by the clinical circumstances:

LINK
(a) Regimen for outpatient induction of methadone (page 23)

- Where a patient has already discontinued their prescribed opioids (e.g. disrupted supply or treatment), or where the patient must suddenly discontinue their prescribed opioids, the general recommendations for methadone induction is as described in regimen (a) above ;
- The general principle for most patients is to taper off the prescription opioid medications (e.g. by 25% of total dose every 5-7 days), and taper onto methadone by an equivalent amount [see Appendix 8], with dose adjustments based on assessment of intoxication, withdrawal, concurrent pain, and other substance use.

(c) Recommended approach to transfer patients from buprenorphine to methadone

Wait 24 hours after the last dose of buprenorphine before commencing methadone. An initial methadone dose of 20 to 30mg is appropriate for patients transferring from daily buprenorphine doses of 8mg or less, and 40-60mg is appropriate for patients transferring from buprenorphine doses of 12mg/day or greater |C|.

A4.2.2 Buprenorphine

Key principles:

1. Patients choosing buprenorphine should be commenced on the combination preparation (buprenorphine-naloxone) unless pregnant or breastfeeding [link to pregnancy section] or with a proven allergy to naloxone. This is an abuse deterrent strategy as buprenorphine-naloxone combination preparations are less likely to be injected than mono preparations containing only buprenorphine |★★|. Furthermore, it is easier to supervise the dosing of the film preparation, compared to tablets, of buprenorphine-naloxone.

LINK
A7.1 Pregnancy and breastfeeding
Availability in 2.1.2

A4 Substitution treatment

2. As a partial agonist, buprenorphine is a safer opioid than methadone with regard to the potential for over-sedation, respiratory depression and overdose. Hence, dose increases can be more rapid and, in general, most patients can achieve their target dose within two to three days |★★★|.
3. Buprenorphine has higher mu opioid receptor affinity and lower intrinsic activity than most other opioids (including heroin, morphine, methadone, oxycodone). As such, it can cause precipitated opioid withdrawal symptoms if given too soon after a recent dose of a full agonist. This is because buprenorphine displaces the agonist but has lower activity as a partial agonist, which can be experienced as precipitated withdrawal |★★★|.

LINK
Precipitated withdrawal in 2.1.2

4. The general principle for safe induction is that the first dose of buprenorphine should be delayed until there is incipient withdrawal |★★★| as assessed by a suitably trained clinician or measured by a validated scale or scales that assess both objective signs and subjective symptoms (e.g. the Clinical Opiate Withdrawal Scale.
   - Initiating buprenorphine for patients using short-acting opioids such as heroin, morphine (other than sustained-release preparations), codeine or oxycodone is usually not associated with severe precipitated withdrawal.
   - Use of the prescribed opioid should be ceased prior to initiation of buprenorphine to avoid precipitated withdrawal. Transfer from slow-release opioid preparations (sustained-release morphine, hydromorphone) to shorter-acting preparations for several days prior to transfer to buprenorphine is recommended.
   - Transfer from long-acting opioids such as methadone can be more difficult due to risk of precipitated withdrawal; recommendations for this are described separately below.

LINK
Appendix 2: Assessment of opioid withdrawal

LINK
(b) Transfer to buprenorphine from pharmaceutical opioids (page 26)

(a) Recommended induction regimen for outpatients using heroin and/or short-acting pharmaceutical opioids.

- Initial doses should be supervised, and a clinician (doctor, nurse, pharmacist) should review the patient daily during the first few days of treatment while the dose is stabilised. The review provides an opportunity to assess intoxication (e.g. sedation, constricted pupils) or withdrawal symptoms, side effects, other substance use and the patient's general well-being.
- Defer the first dose of buprenorphine until the patient is experiencing mild to moderate withdrawal (anxiety, abdominal or joint pain, dilated pupils, sweating). The use of a validated rating scale such as the Clinical Opiate Withdrawal Scale (COWS) can be helpful:
  - For the patient with mild withdrawal (subjective symptoms but no signs of opioid withdrawal that would produce a score less than 8 with the COWS), provide an initial dose of 4mg, with the possibility of a subsequent dose of 4mg after 1-2 hours ('split dosing' reduces the risk of precipitated withdrawal);
  - For the patient with moderate or severe withdrawal at the time of the first dose, an initial dose of 8mg is appropriate;
  - Lower doses (e.g. 2 or 4mg total on day 1) are suited to those with low or uncertain levels of opioid dependence, with high risk polydrug use (alcohol, benzodiazepines) or with other severe medical complications. Seek specialist advice if concerned |C|. ✦

LINK
Appendix 2: Assessment of opioid withdrawal

A4 Substitution treatment

- On subsequent days, the buprenorphine dose can be increased by 2, 4 or 8mg increments, with upper limits of 16mg on day 2 and 24mg on day 3. Slower dose increments (as used for methadone) are not required, and indeed dose increments that are too slow are associated with higher rates of treatment drop-out |★★|.
- Doses should be adjusted following review of the patient – assessing side effects, features of withdrawal (suggesting not enough buprenorphine) or intoxication (suggesting too much buprenorphine or other drug use), ongoing cravings and substance use.
- Higher and more rapid dose increases can be achieved in consultation with an addiction specialist, and/or in inpatient settings with closer monitoring. ✦

When commencing a patient on buprenorphine, take account of pharmacy availability for supervision of dosing and monitoring of response. If 7day pharmacy services are not available, the commencement of treatment should be timed so that induction is well underway before the first day of unsupervised dosing. With buprenorphine it is possible to prescribe a double dose on the first weekend of treatment as an alternative to a takeaway dose if there is no 7day pharmacy service.

(b) Recommended buprenorphine induction regimen for patients using methadone or sustained-release pharmaceutical opioids.

Transfer from methadone (or long-acting pharmaceutical opioids) to buprenorphine may occur for a variety of reasons:

- As a first step in an attempt to withdraw from substitution treatment;
- To take advantage of potentially greater flexibility with buprenorphine-naloxone (alternate day or unsupervised dosing);
- Patient ‘not responding’ to methadone treatment;
- Side effects or drug interactions with methadone.

However, such transfers can be associated with complications, including:

- Precipitated withdrawal on initiating buprenorphine
- Destabilisation of the patient during transfer (including opioid or other substance use, or their medical, psychiatric or social condition);
- Onset of side effects from buprenorphine; and
- Failure to transfer and stabilise on buprenorphine.

LINK
Precipitated withdrawal in 2.1.2

Treatment setting, capacity for frequent monitoring and dosing, staff training and experience, ability to access specialist addiction treatment services or inpatient beds may also have a significant bearing on transfer decisions and outcomes.

Decisions regarding transfer should be made collaboratively by patients and service providers, and involve carers as appropriate. The decision should include an examination of the potential benefits and risks of the transfer |C|.

A4 Substitution treatment

Patients at low risk of complications can be transferred to buprenorphine in outpatient (including primary health care) settings. Patients need frequent monitoring and buprenorphine should be dispensed in multiple doses over the first 4 to 6 hours of the transfer – if this cannot be coordinated in a primary care setting, referral to or consultation with specialist services is recommended. ✦

A low risk of complications during transfer to buprenorphine is indicated by:

- The patient experiencing withdrawal with their current methadone dose, and methadone doses less than 60mg/day;
- No unsanctioned opioid use or unstable use of other drugs;
- No severe medical or psychiatric conditions that may be destabilised during transfer;
- Stable and supportive social conditions;
- No complications during any previous transfer attempts; and
- Good understanding by the patient of the transfer process.

Strategies should be put in place to address any risk factors for complications during transfer. This may involve gradual methadone dose reductions, stabilising other drug use, health or social problems, and may take several weeks or months to achieve.

Where the risk of complications cannot be reduced to an acceptable level, as indicated by the dot points above, specialist referral is recommended. ✦

Transfers to buprenorphine for patients considered at 'high risk' for complications should only be undertaken where there is capacity for:

- Frequent monitoring under medical supervision;
- Supportive care;
- Regular doses of buprenorphine and symptomatic medication as required; and
- Transfer to an inpatient unit in the event of severe complications, or where appropriate supportive care is not available in an outpatient setting (for example, patients with unstable medical, psychiatric or social conditions or medical support for transfers from high doses of methadone).

Experience with methadone to buprenorphine transfers has shown that the key is delaying the first dose of buprenorphine until there is clear evidence of the onset of withdrawal, as determined by a validated assessment instrument |C|. These guidelines give an indication of relevant scores with the Clinical Opiate Withdrawal Scale (COWS) and the Subjective Opiate Withdrawal Scale (SOWS), which are the rating instruments that are most appropriate for use in generalist settings. Withdrawal often does not occur until more than 24 hours after the last dose of methadone. The size of the last dose of methadone is less important than the time since the last dose, as determined by withdrawal.

Where possible, the patient should be reviewed in the week prior to the proposed transfer date, preferably prior to their daily methadone dose to allow the assessment of withdrawal severity. Other factors affecting the risk of complications and the patient's understanding of the process should be assessed at the same time, and plans for the transfer should be reviewed.

A4 Substitution treatment

On the proposed day of transfer, assess the patient prior to any medication including recent substance use, withdrawal severity and general health. Patients should be monitored (withdrawal severity, vital signs) regularly over a 4 to 8 hour period and an initial dose of 2mg buprenorphine administered when moderate withdrawal is apparent (COWS≥13, SOWS≥16). An additional dose of 6mg buprenorphine can be administered one hour later if the initial dose does not precipitate withdrawal.

Supplementary doses can be administered every one to three hours according to withdrawal severity:

- 0mg if there is no or minimal withdrawal (COWS<6, SOWS<8);
- 4mg if there is mild withdrawal (COWS 6-12, SOWS 8-15);
- 8mg if there is moderate to severe withdrawal (COWS≥13, SOWS≥16).

During the transfer ensure supportive care (reassurance, hydration). Symptomatic medication (e.g. metoclopramide, hyoscine butylbromide, low dose sedatives) may be helpful for persistent and severe withdrawal discomfort.

Precipitated withdrawal is indicated by a sustained and marked increase in the severity of withdrawal within the initial 3 to 6 hours of the first buprenorphine dose (e.g. COWS increased by >6, SOWS increased by >8). The general approach to the management of precipitated withdrawal is to continue buprenorphine dosing; symptomatic medication (metoclopramide, NSAIDs, hyoscine butylbromide, low dose sedatives) should also be considered. Specialist consultation is recommended if precipitated withdrawal is suspected. Onset of withdrawal, or marked increases in withdrawal more than 6 hours after buprenorphine may reflect under-dosing rather than precipitated withdrawal.

Patients should be reviewed daily for the next 2-5 days or until comfortable, including assessment of withdrawal severity, recent substance use, adverse events, general progress and any concerns they may have. Buprenorphine doses should be administered under supervision as follows:

- Patients in moderate to severe withdrawal (COWS≥13, SOWS≥16) the total dose of the previous day, plus 8mg, up to a maximum of 32mg;
- Patients in mild withdrawal (COWS 6-12, SOWS 8-15) the total dose of the previous day, plus 4mg, up to a maximum of 32 mg;
- Patients with no or minimal signs of withdrawal (COWS 0-5, SOWS<8) the total dose of the previous day, plus 4mg, up to a maximum of 32mg.

Experience suggests that most patients transferring from methadone doses greater than 30mg will require buprenorphine doses of at least 8mg on day 1, and often will require 16-32mg on the first day, especially if transferring from higher methadone doses. Doses may need to be adjusted according to other substance use, side effects or other medical conditions, for which specialist advice is recommended.

A4 Substitution treatment

Many patients will feel uncomfortable for the first 2 to 5 days on buprenorphine, with mild opioid withdrawal symptoms, headache, dysphoria, anxiety and sleep disturbances:

- Reassure patients that symptoms tend to subside with time, and provide supportive care;
- Ensure the buprenorphine dose is adequate;
- Symptomatic medications (metoclopramide, hyoscine butylbromide, low dose sedatives) may be used for a limited time (typically 1-3 days) for those patients not coping with persistent symptoms.

A minority of patients find buprenorphine unsatisfactory and will request transfer back to methadone.

A4.3 Delivering safe and effective agonist maintenance treatment

A4.3.1 Optimising medication dosing regimens

Patient input to treatment decisions, including determination of dosing levels, promotes a good therapeutic relationship by enhancing patient trust and self-responsibility. Doses should be tailored to each patient, adjusting the dose in response to:

- Medication effects (intoxication or sedation from too high a dose, withdrawal from an inadequate dose);
- Side effects – many opioid side effects subside in the first 2 to 4 weeks of treatment, but some are persistent and may require dose adjustment (seek specialist advice if uncertain);
- Continued drug use – increasing doses of methadone or buprenorphine is often an effective response to unsanctioned opioid use, but has a limited role in addressing use of other drugs (e.g. alcohol, cannabis, benzodiazepines, stimulants);
- Patient report of dose adequacy and treatment goals.

Methadone

Adjust doses by 5 to 10mg at a time, as needed, with at least three days between each dose adjustment.

LINK
2.3.2 Effectiveness of substitution treatment

Methadone in doses of 60mg/day or greater is more effective than lower doses in terms of retention in treatment, reduction in unsanctioned opioid use and associated high risk behaviours |★★★★|.

Most patients require methadone doses in the range 60-120mg/day to achieve stabilisation and this should be regarded as an appropriate range for maintenance doses. A small proportion of patients may require higher (e.g. up to 150mg/day) or lower (e.g. 30-40mg/day) doses to achieve their treatment goals. Doses above 150mg/day are generally associated with little additional benefit and increase the risk of dose-related adverse events |C|. Specialist referral is recommended for patients seeking methadone doses greater than 150mg/day |C| for an investigation of the reasons for the high dose requirement. ✦ There may also be jurisdictional requirements for approval of doses greater than 120mg/day.

A4 Substitution treatment

Some patients may benefit from 'split' or multiple daily doses of methadone. In particular:

- patients using methadone for chronic pain management typically require methadone doses every 8 to 12 hours for effective analgesia;
- patients who are rapid metabolisers of methadone due to genetic variation or interaction with medications that induce CYP enzymes usually benefit from split dosing rather than higher doses administered once a day – in these cases there is some role for therapeutic monitoring of methadone plasma levels, usually in consultation with an addiction specialist; and
- pregnant women.

LINK
Drug interactions in 2.3.7

Safety issues, such as diversion of doses and use of other drugs, must be considered prior to authorising split dosing, and a second opinion or specialist referral is recommended. ✦

LINK
Managing pregnancy in 2.6.3

Buprenorphine

Adjust doses by 2 to 8mg at a time as needed. Evidence indicates that buprenorphine doses of 8-16mg are superior to lower doses in terms of retention in treatment, reduction in unsanctioned opioid use, and associated high risk behaviours.|★★★★|

LINK
2.3.2 Effectiveness of substitution treatment

Most patients require daily buprenorphine doses in the range 12-24mg to achieve stabilisation, although some patients require higher (e.g. up to 32mg/day) or lower (4-8 mg/day) doses to achieve their treatment goals. Doses greater than 16mg are associated with increased duration of action, with little or no increase in the degree of opioid effect. The maximum possible dose of 32mg is a regulatory and manufacturer's limit |R|. Higher doses may be associated with dose-related adverse events; specialist consultation is recommended for patients seeking doses greater than 32mg. ✦

LINK
2.1.2 Buprenorphine

The characteristics of buprenorphine allow a wide range of dosing regimens, from several times daily to once every two or three days. The main reasons for considering reduced frequency dosing are convenience for patients, and reduced staffing requirements for supervised dose administration.

Patients interested in less than daily dosing should first be stabilised on daily dosing before trying alternate-day dosing for two weeks. If this is successful, the patient can then be tried on a three-times-a-week regimen. If a patient cannot be stabilised on such dosing regimens due to the onset of withdrawal, cravings, side effects or features of intoxication, they should be returned to a more frequent dosing regimen.

Alternate-day or four-times-a-week regimens involve attending the pharmacy for dosing on alternate days (i.e. a dose every 48 hours), or attending four times a week (with 3x48 hour doses and 1x24 hour dose each week, e.g. Mon, Tues, Thurs, Sat). The advantage of the latter approach (4 times a week) is that the patient attends regularly each week, with less likelihood of attendance errors on the patient's part and dosing errors by the pharmacist.

The dose dispensed for a 48-hour period is initially double the normal daily (24 hour) buprenorphine dose (to a maximum of 32 mg at a time).

The patient should be reviewed following the first or second 48-hour dose. Dose adequacy can be inferred if patients report being as comfortable on the second day as on the first, sleeping as well on the second night as on the day of dosing, and no more cravings on the second day than on the first.

A4 Substitution treatment

If the patient reports onset of withdrawal or cravings, or sleep difficulties in the second day then the 48-hour buprenorphine dose should be increased. If the patient reports features of intoxication from the dose of buprenorphine during its peak effects (normally at about four hours) the 48-hour dose should be reduced.

Patients on low doses of buprenorphine may find that double the dose does not last for 48 hours. Patients on reducing doses of buprenorphine may need to switch to daily dosing as the dose becomes lower (i.e. below 4mg). Some patients are not comfortable with double dose when switched to less than daily dosing.

Some patients may tolerate three-times-a-week dosing with buprenorphine, reducing the inconvenience and costs of treatment further. This should be attempted once a two-week trial on four-days-a-week dosing has been shown to be successful. If the 24-hour buprenorphine dose is less than 12mg, the 3-day dose is three times the 24-hour dose. If the 24-hour dose is 12mg or greater, the 3-day dose should be 32mg.

Takeaways and unsupervised dosing

In these guidelines, “takeaways” are defined as involving the provision of medication to be taken from the dispensing point for later consumption. “Unsupervised dosing” is the consumption of medication that is not witnessed by a responsible adult[6]. “Takeaways” suggests “unsupervised dosing”, but it is possible that “takeaways” could be provided for administration under the supervision of a responsible adult.

In general, treatment of opioid dependence with methadone or buprenorphine is based on daily, supervised dosing at a pharmacy or clinic. Decisions on the provision of takeaway doses need to strike a balance between risk management and patient autonomy, with particular consideration of the risks to others and the community in general. The approval of takeaway doses is at the discretion of the prescriber. When used appropriately, takeaway doses can reinforce therapeutic engagement with mitigation of the risks to the patient, their family and the community.

Supervised dosing provides:

- Greater adherence to the medication regimen, with less diversion to others and less misuse such as injecting of medication;
- Less risk of overdose from dosing of intoxicated patients, use of excessive doses, or following treatment interruption (missed doses); and
- Daily structure and routine that can be important for many patients early in treatment.

However, many patients find the requirements of daily supervised dosing intrusive and not compatible with community re-integration through activities such as work or study. The provision of takeaways and unsupervised dosing may:

- Improve patients’ reintegration into normal daily activities and routines by reducing the inconvenience of regular pharmacy attendance (particularly for workers, or in regional or rural areas);
- Reduce the cost of treatment to patients by reducing dispensing fees and travel costs;

[6] A ‘responsible’ adult would generally be a person who is not misusing alcohol or other drugs and is able to adequately assess the appropriateness of administering methadone or buprenorphine

A4 Substitution treatment

- Enhance treatment outcomes, in which positive behaviours (e.g. regular attendance for appointments or dosing, cessation of other substance use) are linked to increased access to takeaway doses, consistent with the principles of contingency management;
- Improve patient autonomy in the management of their medication and treatment in general, consistent with the principles of chronic disease management;
- Reduce stigma associated with attending dosing points, particularly where there are concerns regarding confidentiality for the patient.

The extent of risk depends on the frequency and number of consecutive takeaways and the formulation of medication being provided as takeaway doses. The safety profile of buprenorphine enables greater flexibility in dosing, particularly as buprenorphine-naloxone which is less liable to diversion or misuse than the buprenorphine mono preparation. However, the evidence base on takeaway doses is very limited with most studies of substitution treatment occurring in the context of supervised dosing. For further detail on takeaways and unsupervised dosing and approaches to mitigation of the associated risks, see sections A10.4 and 2.3.6

LINK

A10.4 Criteria for takeaways and unsupervised dosing

Takeaways and unsupervised dosing in 2.3.6

Intoxicated presentations

Patient safety is the key consideration in responding to those who present for dosing while intoxicated due to opioids, alcohol or other drugs. Patients should be made aware at the commencement of treatment that medication will be withheld in the event of intoxication.

LINK

Appendix 6: Signs of intoxication with commonly used drugs

Patients should always be assessed by the person dispensing the dose (nurse or pharmacist) for signs of intoxication before the dose is given. Patients who appear intoxicated with CNS depressant drugs should not be dosed or given a takeaway dose of methadone or buprenorphine.

Patients can be asked to re-present later in the day (or the following day) for dosing. The prescribing doctor must be notified to determine the need for the patient to be assessed by the prescriber prior to the next dose being administered.

Patients with a history of repeated presentations for dosing while intoxicated should be reviewed by the treating doctor and the treatment plan reconsidered.

Missed doses

Repeated missed doses (patients not taking their regular dose of methadone or buprenorphine) can be associated with reduced opioid tolerance, opioid withdrawal and/or use of other substances, which in turn impact on treatment safety and effectiveness. There are particular safety concerns for:

- patients recommencing methadone after missing doses on four or more days because of reduced opioid tolerance and risk of overdose on recommencement of methadone, particularly if other sedative drugs have been used; and
- patients recommencing buprenorphine after missing doses on four or more days because of precipitated withdrawal if the patient has been using opioid agonists (e.g., heroin, morphine, methadone).

A4 Substitution treatment

Therefore, when a patient misses doses on four or more days a review or consultation with the prescriber, or a clinician experienced in treatment of drug and alcohol problems, must occur before the next dose of medication is administered. The following procedures are recommended.

Doses missed on 1, 2 or 3 consecutive days

A clinician experienced in the treatment of drug and alcohol problems should review the patient prior to dosing, including:

- the circumstances around the missed doses, including reasons for non-attendance;
- recent substance use and clinical presentation at dosing (including evidence of intoxication or withdrawal);
- any relevant medical, psychiatric or social issues.

Normal dosing can be resumed if there are no concerns regarding intoxication, significant withdrawal or other clinical issues.

- Intoxicated patients should not be dosed with methadone or buprenorphine.
- The dosing clinician should consult the prescriber or a clinician with experience in the treatment of addiction if the patient presents in severe opioid withdrawal or other significant medical or psychiatric conditions.

Doses missed on 4 or 5 consecutive days

The dosing clinician should assess the patient (as above) and attempt to contact the prescriber.

If the prescriber can be contacted, a dose of methadone or buprenorphine may be authorised subject to the prescriber being able to forward a legal prescription to the dosing site. A nurse or pharmacist cannot legally dispense any dose other than that documented on the prescription.

- For methadone patients, the prescribed dose for that day should, in general, be equivalent to half the regular daily methadone dose and should not exceed 40mg. Patients should be monitored by a clinician on subsequent days prior to dosing, aiming to return to the regular dose within 5 to 7 days, usually in increments of up to 20mg per day.
- For buprenorphine patients, a prescription equivalent to half the regular daily dose, but not exceeding 8mg, should be issued for that day. Patients should be monitored by a clinician on subsequent days prior to dosing, aiming to return to the regular dose within 2 to 3 days, usually in increments of up to 8mg per day.

In the event that the prescriber cannot be contacted or is unable to provide a valid prescription, the patient cannot be dosed. The patient should be referred to their prescriber for review and to re-initiate treatment.

Doses missed on more than 5 consecutive days

The patient must be reviewed by the prescriber prior to recommencing treatment. Methadone dose induction should commence low (<40mg/day) with careful subsequent titration, as described in section A4.2.1(a).

LINK

A4.2.1 Methadone (a) Recommended regimen for outpatients with unsanctioned use of opioids

A4 Substitution treatment

Reviewing patients who repeatedly miss doses

A small proportion of patients have poor attendance for dosing. This may be due to ambivalence about treatment, access (e.g. transport, work commitments, limited dosing hours) or medical issues (mobility problems, cognitive impairment). These patients should be reviewed by their prescribing doctor to find out why, and whether the reasons for missing doses can be addressed. Options for improving treatment adherence may include changes in dosing sites or takeaway access. Some patients who repeatedly miss doses may report that their doses of methadone or buprenorphine are inadequate. It is recommended that regular attendance be encouraged prior to any dose increases.

A4.3.2 Clinical review and monitoring

Clinical review provides an opportunity to assess:

- The patient's general presentation, the quantity and frequency of any substance use since the last review, general health and wellbeing, social circumstances, living environment and relevant risk factors (child protection, harm to self or others, domestic violence, overdose, blood-borne virus risk);
- The current medication conditions, including attendance for dosing, adequacy of medication dose, side effects, takeaways, frequency of reviews, monitoring and counselling services; and
- Treatment progress against the treatment plan.

LINK

3.5 Reviewing treatment progress

The frequency of clinical review will vary according to the patient's circumstance and stage of treatment, and jurisdictional requirements. In general, until stabilised, most patients should be reviewed at least once a month by a clinician involved in medication-assisted treatment of opioid dependence. More frequent reviews (e.g. every week) should occur early in treatment, during periods of instability, or during withdrawal attempts. Patients who are stable in long-term treatment may be seen less frequently.

A comprehensive review that includes examining longer-term goals and treatment planning covering long-standing health issues, screening and prevention activities, and consideration of cessation of medication should occur at least once every six months or when there is a change in the patient's circumstances.

It is appropriate to review treatment of patients who have been on high doses of methadone or buprenorphine for long periods of time to determine whether that dose is still necessary. Assess patient stability, discuss treatment progress and actively monitor the implications of any dose reductions in terms of re-emergence of withdrawal symptoms, cravings or unsanctioned opioid use **|C|**.

Some patients may continue on low doses of medication (<30mg/day methadone or 2mg buprenorphine) for long periods and be resistant to cessation of treatment. The key is stability. It is appropriate to discuss withdrawal with the patient, but if they are stable and comfortable, there is no reason to encourage cessation of medication, and there are good reasons to maintain the medication.

A4 Substitution treatment

There are instruments available to aid in the assessment of response to opioid substitution treatment, including providing patient feedback and clearly charting progress in treatment. Emphasis should be placed on the benefits that can be achieved in conjunction with maintenance treatment. Placing undue emphasis on abstinence can devalue these benefits and overwhelm those patients for whom abstinence seems an unachievable goal. Treatment progress is measured by tracking improvements in severity, complexity and the development of recovery capital. Integrating medication assisted treatment with health interventions, social supports and participation in treatment will build resilience.

LINK
Glossary of terms and abbreviations

Urine drug screening

Urine drug screening can be used to identify use of substances in recent days, up to six weeks depending on the type of drug used, the dose and duration of use and individual metabolism.

LINK
See Appendix 7 for selected drug detection estimates

Urine drug screens are an important means to:

a) enhance the validity of patients' self-reported use of substances,

b) identify substances not reported by the patient that may assist diagnosis and management (for example, by identifying amphetamine or cannabis use in a patient developing features of psychosis), and

c) assist in determining eligibility for takeaway or unsupervised dosing.

LINK
A10.4 Criteria for takeaways and unsupervised dosing

Clinicians should check with their local pathology service for information on the screening tests used, the drugs or drug classes tested for and the cut-offs applied. The Medicare Benefits Schedule imposes limits on the number of drug screens that will be funded, currently 36 per year [7].

Urine drug screening should be used with caution. Screening tests may provide false positive or false negative results; they can be confrontational for patients who do not understand their purpose, and cost must be considered. Clinicians should liaise with their local pathology service to obtain optimal interpretation of screening tests and to discuss whether further testing is necessary for an individual patient's management. It should be noted that the level of reimbursement does not cover confirmatory testing by specialised techniques such as gas chromatography/mass spectrometry (GC/MS). As with any investigations, the use of screening tests should be based on clinical indications, and not performed routinely due to "program rules".

Benchtop (dipstick) testing systems have limitations, including cost and the range and amount of substances able to be detected, but they provide a useful, quick approach where it is desirable to confirm recent drug use.

Directly observed urine samples are intrusive and impact negatively on therapeutic engagement. As such, they should be avoided wherever possible. Other mechanisms, such as management of toilet facilities, checking sample temperature and testing for non-human sources or dilution, are generally sufficient to ensure the sample is genuine. However, directly observed samples may be a requirement in some situations.

[7] See http://www.mbsonline.gov.au/ and search for item 66626. Accessed 15 March 2013..

A4 Substitution treatment

The appropriate frequency of urine drug screening is not readily determined and is likely to change in the course of treatment. As such the frequency of urine drug screening is primarily based on the judgement of the prescribing doctor. An intermittent schedule of random testing is adequate for program requirements and patient safety – the uncertainty and unpredictability of screening is likely to ensure more useful information than a system of frequent screening.

Continued drug use

Individuals with continuing high-risk patterns of drug use, or concomitant medical, psychiatric or social problems, may require more frequent review.

Continued high risk drug use is evidenced by:

- presentations for dosing or review when intoxicated;
- overdoses;
- chaotic drug using behaviour;
- deteriorating medical or mental status due to drug use.

Continued drug use can affect stability and treatment progress and place the patient at risk of:

- relationship, social and employment problems;
- contracting infectious diseases;
- involvement in crime.

Attempts should be made to stabilise such patients. A review is required of their psychosocial interventions and supports, precipitants to continued drug use, and medication regimens.

An adequate dose of medication should be prescribed and the clinician must ensure that the patient is taking the medication as prescribed, which may require:

- ceasing takeaway doses;
- ensuring supervised consumption;
- daily dosing regimens of buprenorphine; and
- drug testing (e.g. on-site urine drug screening).

If attempts to stabilise drug use are not successful, review the medication regimen and consider non-pharmacological treatment options (e.g. therapeutic communities, counselling and support) when:

- there is little or no response to an increase in medication;
- the patient is already on a high dose of medication;
- an increase in dose is considered ‘unsafe’ by the prescriber;
- the patient is persistently diverting their dose;
- the patient attends irregularly, frequently missing scheduled doses; or
- the patient persistently attends intoxicated.

A4 Substitution treatment

For patients receiving buprenorphine, optimise the dose to ensure adequacy and seek to stabilise other drug use. For patients receiving methadone, consider changing to buprenorphine because of the greater safety when used in combination with other drugs and easier withdrawal if this becomes necessary.

Consideration should be given to the risks of prescribing methadone or buprenorphine in the presence of other drug use against the risks of ceasing treatment:

- if the patient's safety is not at risk from ongoing drug use it will generally be in their interest to persist with treatment;
- if the risks of combining methadone or buprenorphine with other drug use outweigh the benefits of substitution treatment to the patient, arrange the patient's gradual withdrawal from methadone or buprenorphine. As there is increased risk of death following involuntary withdrawal of treatment, this should be considered a response of last resort.

A4.4 Safety

Adverse events (e.g. suspected drug interactions, allergic reactions, problems associated with naltrexone implants) should be reported to the Therapeutic Goods Administration.

LINK
See www.tga.gov.au/daen

A4.4.1 Overdose

The risk of overdose is greater with methadone, but is not insignificant with buprenorphine. Induction onto methadone is associated with increased risk of overdose until a stable dose is achieved that will reduce craving and reduce the effect of any additional opioid use. Use of central nervous system depressants such as benzodiazepines and alcohol in conjunction with methadone or buprenorphine is a significant risk factor in many overdose events. In the event of persistent high dose benzodiazepine use (50mg diazepam equivalent per day), consider transferring the patient to buprenorphine to reduce the risk of overdose |C|. Patients and their families (subject to appropriate consent from the patient) should be given information on prevention and management of overdose |C|.

LINK
Overdose in 2.3.7
A4.2.1 Methadone induction
Appendix 10: Prevention and management of opioid overdose

A4.4.2 Driving

National guidelines on fitness to drive[8] include the following advice on opioid dependence:

"For people treated for opioid dependency, risk of impairment due to unsanctioned use of opioids or other substances is a consideration. Short-acting opioids, particularly parenteral forms, may cause fluctuation in blood levels of opioids, which would be expected to be incompatible with safe driving. People using these agents should be referred for assessment by an appropriate specialist such as an addiction medicine specialist or addiction psychiatrist. People on a stable dose of buprenorphine and methadone for their opioid dependency may not have a higher risk of a crash, providing the dose has been stabilised over some weeks and they are not abusing other impairing drugs."

Jurisdictional regulations on fitness to drive should also be considered.

LINK
Driving in 2.6.11
Appendix 11: State and Territory Government Services

[8] *Assessing fitness to drive for commercial and private vehicle drivers: Medical standards for licensing and clinical management guidelines*. Austroads Ltd March 2012. Available from www.austroads.com.au. Accessed 5 April 2013.

A4 Substitution treatment

A4.4.3 Comorbid medical conditions

Conditions that affect hepatic function and may require dose adjustment, transfer to buprenorphine or cessation of medication, include liver failure, alcohol dependence and acute hepatitis. Specialist consultation should be sought. ✦

LINK
2.6.8 Infections in injecting drug users

Patients with signs of acute or decompensated chronic liver disease (jaundice, encephalopathy, oedema) should undergo a full battery of liver function tests before being considered for substitution treatment, with regular retesting during treatment.

Mild asthma and emphysema are not contraindications to substitution treatment and changing the dose of substitute medication is generally not necessary, but it is appropriate to review other factors that might contribute to respiratory distress |C|. If concerned, seek specialist advice or referral ✦.

A4.4.4 Cardiac function

Background

The QTc interval is the measure of time between the onset of ventricular depolarisation and completion of ventricular repolarisation. A delay in ventricular repolarisation (identified as a prolonged QTc interval) can provoke arrhythmias, such as ventricular fibrillation and torsades de pointes, associated with sudden cardiac death.

LINK
2.3.7 Prolongation of QTc interval

The QTc interval varies depending on heart rate, age and gender, but an interval of 450ms or less in males and 470ms or less in females is considered low risk and within normal range. An interval that is between 450 and 500ms in men or 470 and 500ms in women is considered mildly elevated, while anything over 500ms is severe prolongation. The risk of severe cardiac arrhythmias increases substantially with a QTc interval that is greater than 500ms.

Prologation of the QTc interval is a potential issue patients treated with methadone |★★| and, less commonly, buprenorphine.

Assessment prior to initiating methadone

There is a limited role for routine electrocardiography (ECG) screening of patients seeking to commence methadone treatment, due to the potential delays in initiating treatment, likely poor adherence and associated costs to service providers and patients.

Indications for ECG assessment prior to commencing methadone are:

- previous history of QTc prolongation (for any reason);
- clinical manifestations of QTc prolongation or cardiac arrhythmias (syncope, palpitations, dizziness); and
- significant other risk factors for QTc prolongation (consider drug interactions and family history of unexplained sudden death).

A4 Substitution treatment

Such patients should be informed of the potential risks of QTc prolongation and methadone, and the benefits of ECG assessment prior to commencing methadone.

LINK
2.3.7 Prolongation of QTc interval

Clinicians should balance the risk of deferring commencement of methadone treatment if there are to be significant delays or other barriers (e.g. patient reluctance) in conducting an ECG assessment. Failure to initiate methadone treatment and treatment drop-out may place the patient at greater risk of cardiac and other health problems associated with untreated opioid dependence.

Routine screening with ECG (to assess for structural heart disease) or genetic testing (for congenital long QTc syndrome) is not indicated in opioid substitution treatment.

Responding to QTc prolongation during treatment

In patients with mildly elevated QTc interval (<500ms) with no clinical manifestations (episodes of syncope, dizzy spells, palpitations or seizures):

- discuss the implications of a prolonged QTc interval with the patient taking into account relevant clinical and family history;
- methadone can be continued, but more frequent monitoring and reduction of other risk factors (such as the use of other drugs that are thought or known to be associated with prolongation of the QTc interval) are recommended;
- if the QTc interval remains prolonged, consider referral to an addiction medicine specialist or cardiologist, a trial of methadone dose reduction, or consider transfer to buprenorphine.

In patients with severe prolongation of the QTc interval (>500ms) or where there are clinical manifestations of QTc prolongation:

- seek advice from an addiction medicine specialist and a cardiologist (more intensive investigation may be warranted);
- strong consideration should be given to a risk minimisation strategy including eliminating or minimising other contributing factors, reducing the methadone dose, transferring the patient to an alternative opioid medication (such as buprenorphine, or morphine in a hospitalised patient) or discontinuing methadone treatment;
- the treatment plan should take into consideration the effectiveness of methadone treatment for the patient, and likely impact of any significant treatment changes on broader substance use and general health and welfare. Informed consent is important in ensuring patient adherence with the proposed treatment plan.

A4 Substitution treatment

A4.4.5 Drug interactions

A number of drug-drug interactions can affect the safety and effectiveness of methadone and buprenorphine treatment. The most significant interactions are those that increase the risk of overdose, either through additive effects on respiratory depression (as occurs with alcohol, other opioid drugs, benzodiazepines, tricyclics antidepressants, sedating antipsychotics and antihistamines) or through reductions in metabolism resulting in increased plasma levels of methadone or buprenorphine.

LINK

A4.4.1 Overdose

A2.1.1 Polydrug use

Drug interactions in 2.3.7

However interactions that result in decreased blood levels and cause withdrawal symptoms are also significant and undermine treatment effectiveness.

Specialist advice and caution are required if medications affecting methadone metabolism ✦ (hepatic CYP450 system) are to be prescribed to patients receiving methadone. Patients require careful monitoring for dose effects, and careful titration of methadone doses (by up to 40% in some casts). Buprenorphine is also metabolised by the CYP450 system, but there appear to be fewer clinically relevant drug interactions with buprenorphine compared to methadone.

Detailed information on the nature, biological basis and evidence of the clinical significance of interactions between buprenorphine, methadone and prescription medications can be obtained from www.opioiddruginteractions.com/.

Methadone can be associated with prolonged QTc interval, and may interact with other drugs (prescribed medications, alcohol and illicit drugs such as amphetamines and cocaine) that also prolong QTc. Lists of medications known to prolong QTc can be found at www.azert.org/. QTc prolongation in methadone patients may also be mediated by medications that increase plasma levels of methadone (CYP450 enzyme inhibitors).

Medications that are known to cause, or may potentially cause, clinically significant interactions when used in combination with methadone or buprenorphine are listed in Appendix 3. These interactions should be avoided if possible, or patients should be monitored and medication regimes adjusted as necessary. Consult with an addiction medicine specialist where there are concerns regarding safety or effectiveness of treatment.

LINK

Appendix 3: Drug interactions

A4.5 Side effects

The side effects of methadone and buprenorphine are largely typical of opioid drugs. The side effects that are most troublesome to patients are excess sweating, dental caries, constipation, sleep apnoea, nausea, drowsiness, osteoporosis and reduced sexual function (loss of libido, impotence). It is important to manage and provide advice to patients on these side effects.

LINK

See https://www.ebs.tga.gov.au/ for product and consumer information

2.3.7 Adverse effects

A4 Substitution treatment

A4.6 Cessation of substitution treatment

Successful cessation of opioid substitution treatment for a patient involves the safe and comfortable withdrawal from their opioid medication without relapse into opioid or other substance dependence. As with any chronic condition, premature cessation of treatment can be associated with relapse and/or deterioration in other aspects of the patient's health and well-being.

Information about cessation of substitution treatment should be provided to patients expressing a desire to cease, and those who have stabilised who may be considering cessation. All patients and treatment providers should address issues regarding treatment cessation at regular intervals (e.g. every 6 months). As with other chronic disorders, periodic review of the need for medication is appropriate, with destabilisation the key indicator of the need for resumption or continuation of medication **|C|**.

The best approach is to plan for cessation once unsanctioned drug use has ceased and other aspects of their health and lifestyle have stabilised with evidence of the presence of significant recovery capital, defined as the sum total of all the personal, social, and community resources a person can draw on to begin and sustain recovery from drug and alcohol problems. Unfortunately many patients will want to withdraw more quickly. Even with a carefully planned strategy for cessation it is important to be alert to evidence of destabilisation **|C|**.

An understanding of the predictors of successful cessation of opioid substitution treatment can provide a framework for patients and clinicians to plan for this process. Such predictors are:

- how withdrawal is attempted
  - gradual rather than rapid dose reductions (over months rather than days or weeks) or sudden cessation;
  - good patient understanding of the process and involvement in decision making;
  - participation in psychosocial approaches addressing coping strategies, risk behaviours, support systems;
  - regular review of progress and plans;
- no unstable or problematic use of alcohol or other drugs;
- stable medical and psychiatric condition
  - attention should be paid to mental health (depression, anxiety) or chronic pain disorders that may be destabilised by withdrawal;
- stable social conditions
  - particularly activities and supports for a drug-free lifestyle; and
- duration in treatment.

A4 Substitution treatment

Most patients take one to two years of substitution treatment to stabilise, but some people can achieve stability more quickly while others will not achieve this optimal state.

Detoxification from substitution treatment is different to detoxification for entry to a relapse prevention treatment.

The most commonly used treatment approach for ceasing OST is to undertake an outpatient gradual taper of the medication over several months, enabling time for patients to adjust to the necessary physiological, behavioural and social changes that arise during this process. Withdrawal severity tends to increase as the dose approaches zero, with peak withdrawal discomfort usually described in the 1 to 4 weeks after cessation of dosing, and low severity symptoms (poor sleep, mood disturbances, cravings) often persists for several months.

Most patients will tolerate a 5-10% reduction of the current methadone dose every 1 to 4 weeks in the dose of their medication, with the rate of reduction varied according to the indications and timeframe for withdrawal **|C|**.

Patients withdrawing from buprenorphine treatment will generally tolerate greater incremental reductions than is the case with methadone. With buprenorphine dose reductions of up to 25% every 1 to 4 weeks can be tolerated provided patient stability is maintained.

The smallest dose available as buprenorphine-naloxone film is 2mg; many patients find it difficult to cease from this level. Australian regulations relating to the prescription and dispensing of medications require that doctors specify the dose of medication to be dispensed, and prescribing in terms of “half a piece of film” is problematic as it is off-label use. Options at this dose range include:

- using alternate day dosing (although lower doses may not hold the patient for 48 hours) or
- converting to buprenorphine tablets and dividing the tablets (which are scored for half doses).

Whatever strategy is used, it is important to monitor the comfort and stability of the patient.

LINK

2.3.8 Completing substitution treatment

A4 Substitution treatment

A4.6.1 Involuntary withdrawal

Conditions under which patients can be involuntarily discharged should form part of contracts at the commencement of treatment and should be reviewed periodically during the entire episode of care. A decision of involuntary discharge should be considered carefully in light of the increased risk of death that this involves.

It is sometimes necessary to discharge a patient from treatment for the safety or well being of the patient, other patients or staff. This may be the result of:

- violence or threat of violence against staff or other patients;
- property damage or theft from the treatment program or dosing pharmacy;
- drug dealing on or near program premises or dosing pharmacy;
- repeated diversion of medication.

In some instances problems may be resolved by transferring the patient to another program rather than discharging them from substitution treatment and all possible options should be considered.

The rates of dose reduction in involuntary withdrawal will depend on the circumstances. Typically in cases of violence or drug dealing withdrawal may be immediate (and may be specified by jurisdictional regulations). However, a gradual taper of medication is preferred where possible. Patients being discharged must be warned about the risks of opioid drug use, of possible reduced tolerance to heroin and subsequent risk of overdose, and informed of other treatment options. This advice should be clearly documented in the patient's clinical record.

A management plan regarding subsequent readmission should be developed for each patient involuntarily withdrawn from the program and recorded in the patient's clinical record. A patient's previous conduct is a helpful guide to likely outcomes of subsequent treatment attempts. This may be helpful in preventing situations where involuntary discharge is the only available course of action.

Relapse prevention: Naltrexone maintenance treatment

Naltrexone is approved for use as an adjunctive therapy in the maintenance of formerly opioid-dependent patients who have ceased the use of opioids such as heroin and morphine. As such, the provision of psychosocial support, focusing on relapse prevention, is an integral component of naltrexone maintenance treatment.

LINK

See www.ebs.tga.gov.au for product information

2.5 Adjunct therapies

A5.1 Pharmacology

Naltrexone is an antagonist at the mu opioid receptor. In doses of 50mg/day, oral naltrexone will attenuate the effects of opioid drugs. In naltrexone maintenance treatment, this attenuation of opioid effects provides support for relapse prevention treatment.

Sustained release and implant preparations of naltrexone are currently not registered in Australia and remain experimental.

LINK

Availability in 2.1.3

A5.2 Effectiveness

The evidence on the effectiveness of naltrexone maintenance treatment is limited by low rates of retention in studies, and the small number of comparable studies. Current evidence indicates no significant difference in treatment retention or abstinence for people treated with naltrexone, with or without adjunctive psychosocial therapy, compared to placebo or psychosocial therapy alone |★★|.

A5.3 Factors affecting treatment selection

Naltrexone is indicated as an adjunctive relapse prevention treatment in people who have withdrawn from opioids, are seeking to remain abstinent, and are capable of giving informed consent to naltrexone treatment.

Given the potential for overdose after relapse, naltrexone treatment is most likely to be useful for those with strong motivation for abstinence, such as:

- people whose continuing employment is dependent on abstinence;
- those who have been using drugs for only a short time;
- when there is a “significant other” (family member, close friend) to administer and supervise the medication; or
- where treatment is monitored in the context of a drug court or other legal diversion program.

Contraindications to naltrexone treatment are:

- current physiological dependence on opioids – those currently physiologically dependent should be offered detoxification or referred to specialist services;
- acute opioid withdrawal – there needs to be a drug-free interval before commencing naltrexone;
- using opioids for chronic pain states – this requires specialist assessment;
- acute hepatitis or liver failure as naltrexone can be hepatotoxic in high doses – the margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only fivefold or less;
- known adverse reactions or sensitivity to naltrexone.

A5 Relapse prevention: Naltrexone maintenance treatment

Patients with signs of acute or decompensated chronic liver disease (jaundice, encephalopathy) should undergo a full battery of liver function tests before being considered for naltrexone treatment, with regular retesting during any treatment with naltrexone.

LINK

2.4.6 Undesirable effects and consequences

In the following situations caution is advised in prescribing naltrexone and assessment by an addiction medicine specialist is recommended.

- Women who are pregnant or breastfeeding as naltrexone is classified as a B3[9] risk in pregnancy.
- Patients concurrently dependent on multiple drugs.
- Patients with impaired renal or hepatic function, as naltrexone and its active metabolite are excreted in urine.
- Patients with major psychiatric illness including major affective and psychotic disorders.
- Children and adolescents as the effects of naltrexone in the treatment of opioid dependence in these populations is also unknown.

A5.4 Initiating treatment

The best approach to initiation of naltrexone maintenance treatment is to manage withdrawal from opioids with small doses of buprenorphine before commencing naltrexone.

LINK

A3.5 Medication approaches for withdrawal

2.2.3 Medications to manage withdrawal

Introduce naltrexone with caution if there is any uncertainty about time of last opioid use |C|. An interval of five days between last buprenorphine and first naltrexone is recommended for generalist settings. If heroin was the last opioid used, an interval of 7 days is recommended, and 10-14 days if methadone was the last opioid used. If a faster transition is desired, seek specialist advice or referral. ✦

Urine drug screening is of little use during naltrexone induction. The best approach is to advise the patient that the first dose of naltrexone may precipitate withdrawal if opioids have been used recently. If there is a risk of precipitated withdrawal due to uncertain recent opioid use, seek specialist advice |C|.

Commence naltrexone at 25mg per day for three days, then increase to 50mg per day if tolerated |C|. Note that the onset of withdrawal triggered by naltrexone can be delayed following buprenorphine treatment.

[9] Under the system established by the Australian Drug Evaluation Committee (ADEC), Pregnancy Category B3 drugs are those that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. For more information go to http://www.tga.gov.au/ and search for the medicines in pregnancy database. Accessed 9

A5 Relapse prevention: Naltrexone maintenance treatment

A5.5 Delivering safe and effective naltrexone treatment

Patients should be provided with information regarding risks associated with cessation of naltrexone and return to opioid use, and in particular, the increased risk of overdose. Some patients may wish to use naltrexone in an intermittent way.

For example:

- a patient may be abstinent, but when facing a high risk situation, will take one tablet
- a patient may want to avoid opioid use most days, but want to take opioid drugs on weekends.

There are serious potential risks with these approaches, including:

- overdose on opioids due to risk of misjudging level of tolerance;
- precipitated withdrawal due to resumption of naltrexone following reinstatement of opioid dependence.

For these reasons, it is appropriate to caution people against irregular use of naltrexone. Furthermore, in some situations it may be prudent to discontinue naltrexone treatment if the patient's level of risk-taking outweighs any observed benefits of the treatment.

Many patients who have relapsed will express a desire to resume naltrexone treatment. However, these patients need to be cautioned that reinstatement of dependence occurs rapidly within days of regular opioid use, and therefore, somewhat unpredictably, resuming naltrexone can precipitate severe withdrawal.

- If it is more than 5 days since the last dose of naltrexone, and the patient has used heroin or other opioids each day since then, recommence on naltrexone as though a new patient requiring detoxification.
- If within 5 days of last naltrexone dose, restart naltrexone under medical supervision – patients may experience withdrawal, but this is usually not severe.
- Restart naltrexone in the morning, at least 24 hours after last use of heroin or other short-acting opioid.
- Commence with ½ tablet (25mg).
- Patients may need symptomatic medication.

A5 Relapse prevention: Naltrexone maintenance treatment

Clinical experience to date has been that patients who relapse and return to naltrexone tend to remain in treatment a relatively short time. After multiple relapses, medical practitioners should seriously consider whether it is appropriate to continue naltrexone treatment, as it becomes increasingly likely that the patient will drop out, and it is preferable to actively manage cessation of treatment than for people to drop out and be receiving no treatment. Alternative approaches such as residential treatment or methadone or buprenorphine maintenance treatment should be discussed.

LINK

2.4.1 Effectiveness of naltrexone treatment

A5.6 Monitoring and review

Patients should be seen regularly while on naltrexone treatment. It is recommended that clinical reviews should be conducted weekly during the first month of treatment, then fortnightly or monthly as required.

Monitoring of compliance and progress should occur at each clinical review:

- assess drug use, for both heroin and other drugs;
- assess compliance with naltrexone regimen;
- assess changes in social functioning and relationships;
- review whether the patient is involved in counselling;
- monitor side effects especially mood.

Naltrexone treatment or, possibly, abstinence from heroin may exacerbate or unmask psychiatric problems, particularly depression, in susceptible subjects. Identification and monitoring of depressive symptoms is desirable, and if there is concern about a patient's mood, psychiatric assessment may be helpful.

Psychosocial support

Psychosocial support is an integral component of medication-assisted treatment. People who are opioid dependent often have complex issues – social, housing, legal, employment, mental health, etc. The first aim of treatment is stabilisation – it is best to delay interventions for relapse prevention and structural behavioural therapies until immediate needs have been addressed.

LINK
2.5 Adjunct therapies

Psychosocial interventions delivered as one-on-one and group sessions – including cognitive and behavioural approaches and contingency management techniques – can add to the effectiveness of medication-assisted treatment. Psychosocial services should be made available to all patients, although those who do not take up the offer should not be denied effective pharmacological treatment.

Psychosocial support should be tailored to the individual and should include issues such as financial management and advice |C|. Psychosocial support also encompasses the promotion of treatment compliance.

Participation in self-help groups (e.g. Narcotics Anonymous, SMART Recovery) should be recommended to patients, but attendance should not be mandatory |C|. The effectiveness of self-help groups is related to participation, not just attendance, and mandatory attendance can be counterproductive.

LINK
2.5.4 Psychosocial support

Issues that may impact on treatment

People who are opioid dependent frequently have a range of health concerns (including dental problems, contraception and sexual health). An integrated, coordinated care approach will ensure a holistic response addressing the issues on an individual basis |S|.

It is important to be aware of cultural and linguistic diversity when treating Aboriginal and Torres Strait Island patients, and migrants to Australia.

Women are more vulnerable to the risk of domestic violence and sexual abuse. They are also more likely to be involved in commercial sex work. They may need advice on sexual health, contraception and parenting skills, and are generally more vulnerable than men. Fear of losing custody of children can be a motivating factor, but can also deter women from seeking treatment. Liaison with child protection agencies may be helpful.

A7.1 Pregnancy and breastfeeding

Maintaining or initiating substitution treatment is the preferred approach to management of opioid dependence in pregnancy. Opioid substitution treatment with methadone or buprenorphine is associated with improved maternal and neonatal outcomes and is a key strategy to link pregnant women who are opioid dependent with antenatal services. While buprenorphine and methadone are both listed as Category C drugs[10], opioid substitution treatment with methadone or buprenorphine remains the treatment of choice for pregnant women. Neither methadone nor buprenorphine appear to be associated with teratogenicity or malformations.

Detoxification is risky in the first trimester due to risk of miscarriage and in the third trimester due to risk of foetal distress and premature labour. Any potential benefit from detoxification, or reduction of dose of medication, must be balanced against the risk of relapse to uncontrolled drug use |C|.

Methadone is safe and effective in terms of consistently better obstetric and perinatal outcomes compared with pregnancies of opioid dependent women not receiving opioid substitution treatment |★★★★|. Overall methadone and buprenorphine are both effective in pregnancy |★★★|; the choice should be made in consultation with the patient. If buprenorphine is used in pregnancy, the mono preparation (Subutex®) is preferable. While the absorption of naloxone is minimal when the combination preparation (Suboxone®) is administered sublingually, the effect of long term low level naloxone exposure on the fetus is unknown. It is recommended not to attempt transfer from methadone to buprenorphine during pregnancy because of the risk of precipitated withdrawal |C|.

LINK

Dose reductions or detoxification during pregnancy in 2.6.3

National clinical guidelines for the management of drug use during pregnancy, birth and the early development years of the newborn, http://www0.health.nsw.gov.au/pubs/2006/ncg_druguse.html

2.6.3 Pregnancy and breastfeeding

[10] Under the system established by the Australian Drug Evaluation Committee (ADEC), Pregnancy Category C drugs are those which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. For more information go to http://www.tga.gov.au/ and search for the medicines in pregnancy database. Accessed 9 April 2013.

A7 Issues that may impact on treatment

If dose reductions or detoxification are to be undertaken during pregnancy these should be implemented in the second trimester.

- Dose reductions should only occur if the pregnancy is stable; liaison with the obstetric team is advised.
- The magnitude and rate of reduction needs to be flexible and responsive to the symptoms experienced.
- Withdrawal symptoms should be avoided as much as possible as they cause considerable distress to the fetus.
- Careful monitoring of the pregnancy and fetus should be undertaken during dose reduction.
- In most instances, dose reductions 2.5-5mg methadone and 2mg buprenorphine per week are considered safe.
- Monitoring should continue after withdrawal off methadone and buprenorphine. If relapse occurs rapid re-induction onto methadone or buprenorphine is indicated.

Outcomes for mother and baby are complicated by polydrug use, especially use of tobacco, alcohol or benzodiazepines. Opioid substitution treatment is associated with neonatal abstinence syndrome, but this can be readily managed with withdrawal management and supportive care. If required, medications such as morphine can be used to manage neonatal withdrawal without long-term sequelae.

The safety and efficacy of naltrexone in pregnancy is not established. If pregnancy is planned, the use of naltrexone should be ceased in advance. For women who become pregnant while on naltrexone, the risks of ceasing should be balanced against the risks of remaining on naltrexone. Specialist advice is recommended. ✦

Antenatal care should be managed, where possible, in collaboration with obstetric services which specialise in the management of substance use problems. Some women may be initially reluctant to advise other health practitioners of the fact that they are on an opioid pharmacotherapy program. Treatment of opioid dependence in pregnancy should optimally be a partnership approach between pharmacotherapy providers and antenatal services.

Pregnancy increases the importance of assessing a wide range of other risk factors, including mental health problems, nutrition, partner violence, housing and the quality of parenting skills.

LINK

Pregnancy and opioid substitution treatment in 2.6.3

Neonatal monitoring in 2.6.3

National clinical guidelines for the management of drug use during pregnancy, birth and the early development years of the newborn http://www0.health.nsw.gov.au/pubs/2006/ncg_druguse.html

A7 Issues that may impact on treatment

A7.2 Age factors

A7.2.1 Adolescents

Treatment of adolescents (generally those aged less than 18), should take into account a broader health and welfare context. The emphasis should be on psychosocial responses, family intervention approaches, vocational issues, and harm reduction, particularly around prevention of sexually transmitted diseases and blood-borne viruses. Nonetheless pharmacotherapy may also be an important component of treatment for some young people |C|.

Pharmacotherapy should only be used after careful assessment of risks and benefits, and in the context of a comprehensive treatment plan embracing various psychosocial approaches |C|. The legal and regulatory requirements of the relevant jurisdiction should be checked before prescribing methadone or buprenorphine to a patient less than 18 years of age.

If pharmacotherapy is used, buprenorphine may be preferred over methadone because of easier cessation. Doses may need to be adjusted from those used for adults.

Depending on their drug use history and social circumstances, adolescents may stabilise quickly on substitution treatment enabling cessation of pharmacotherapy to be considered more quickly than would be the case with adults |C|. However, as with adults, adolescent patients should be monitored for signs of destabilisation and substitution treatment reinstated if necessary.

A7.2.2 Older drug users

The average age of patients in opioid substitution treatment is increasing, making it necessary to give consideration to issues for older patients. In this group, previous substance use, trauma and other factors accumulated from a drug-using lifestyle increase the likelihood of associated problems. Issues around long-term use of high doses of opioids include an impact on the usual ageing process (osteoporosis and sex hormone deficiencies, particularly androgens in men), reduced cognition from repeated hypoxia, risk of falls, changes in pharmacokinetics and poly-pharmacy. Chronic hepatitis C, obesity and smoking-related issues are also likely in this population. Better coordination of care is needed to address the multiple issues.

There is no direct evidence about methadone dosing regimens for maintenance treatment in older adults. However, older drug users are likely to metabolise drugs at a slower rate making lower opioid doses and slower dose titration of methadone advisable in older patients. Large doses of methadone (>150mg/day) are not necessarily best for this group and should be reviewed in consultation with the patient |C|.

A7 Issues that may impact on treatment

A7.3 Comorbid mental health conditions

Treating clinicians need to be skilled in the assessment, management and appropriate referral of people with comorbid mental health problems. Treating only one disorder when a comorbid disorder is present can increase relapse for both disorders. Where significant conditions are suspected, particularly where psychotic features are present, seek a psychiatric opinion. People with significant psychiatric comorbidity are best treated in specialist facilities with linkages between mental health and drug and alcohol services.

LINK

2.6.6 Comorbid mental health conditions

A7.4 Prisoners

This client group warrants special consideration, the aims being to increase wellbeing and social functioning following release, as well as to reduce the risks to community safety and health.

LINK

2.6.9 Prisoners

OST with methadone or buprenorphine is appropriate for prisoners who:

- are receiving OST at the time of imprisonment;
- are opioid dependent at the time of imprisonment and not receiving treatment; or
- continue unsanctioned use of opioids in prison in a manner which constitutes a significant risk of harm.

Confidentiality of medical records of prisoners on pharmacotherapy treatment should receive special consideration so that these records are used for the clinical management of the individual while in custody, and not for custodial purposes. No prisoner should be forced to accept pharmacotherapy or have treatment discontinued for disciplinary reasons.

Appropriate liaison between corrections centres and health services needs to be undertaken to ensure continuity of treatment for those released from prison.

A7.5 Infectious diseases

Vaccinations for hepatitis B and tetanus are recommended. Hepatitis B vaccinations should be administered at 0, 1 and 6 months, in accordance with national guidelines.

Treatment of HIV, hepatitis C and chronic hepatitis B is as effective in people with a history of opioid dependence who are currently engaged in opioid substitution treatment as in other population groups. In people with advanced HIV, hepatitis C or hepatitis B and ongoing opioid dependence, substitution treatment is recommended in conjunction with antiretroviral treatment to facilitate treatment adherence |★★★| and improve outcomes for both conditions.

Drug interactions between antiretroviral medications and methadone, and to a lesser extent buprenorphine, need to be monitored and may necessitate adjustment of medication regimens.

LINK

For current clinical information see www.ashm.org.au

2.6.8 Infections in injecting drug users

A4.4.5 Drug interactions

Drug interactions in 2.3.7

A7 Issues that may impact on treatment

A7.6 Management of pain

When managing mild to moderate acute pain in patients receiving methadone or buprenorphine, it is important not to assume that the maintenance dose of substitution treatment will manage the pain. Both buprenorphine and methadone have analgesic properties but have shorter analgesic interdosing intervals (the analgesic effects of methadone last 8-12 hours). For analgesia, consider non-opioid approaches first. If an opioid is required, either add an opioid analgesic to the substitution treatment regimen (taking into account jurisdictional requirements regarding the prescription of opioid medications for people in opioid substitution treatment), or increase the substitute medication by 10-15% for a limited time (1-2 weeks) and split the dose. For severe, acute pain, higher doses may be required. In an acute care setting increasing the dose of substitute medication by 30% may be appropriate. Specialist advice is recommended if the patient fails to respond to treatment |C|. ✦

LINK

2.6.10 Management of pain

www.racgp.org.au/your-practice/guidelines/silverbook/common-clinical-conditions/pain-management/#1

People with chronic pain receiving methadone or buprenorphine substitution treatment should be managed as for any other patient with non-opioid approaches emphasised. However, there are some notable differences |C|:

- tolerance means that normal doses of opioids are likely to be less effective;
- when prescribing be aware of the potential for aberrant behaviours and use appropriate strategies (monitoring and interval dispensing);
- avoid use of other psychoactive medications for which there is no evidence of effectiveness in pain relief (e.g. benzodiazepines, antidepressants);
- if concerned, seek specialist advice or referral;✦ and
- if prescribing opioids, be aware of relevant jurisdictional regulations and resources available to assist prescribers.

Use caution when continuing pain relief following discharge from hospital and avoid prescription of multiple opioid medications |C|.

Acute and chronic pain can destabilise patients in opioid substitution treatment – vigilance is needed |C|. Tailor the dose of methadone or buprenorphine in chronic pain as with any other medication |C|. Split dosing can be useful in chronic pain.

People with chronic pain conditions who experience dependence related problems may benefit from methadone or buprenorphine maintenance treatment. The patients with chronic pain for whom methadone or buprenorphine maintenance may be considered include those:

LINK

A4.2.1 Methadone

Chronic pain in 2.6.10

- using illicit drugs (heroin) in addition to prescribed analgesics;
- using large amounts of analgesics gained from multiple sources in an unsanctioned way (including by injection); and
- unable to control their analgesic use (taking more and more) despite strategies such as having one nominated prescriber, dispensing small quantities of opioid each time, and dispensing frequently (e.g. daily or every second day).

A7 Issues that may impact on treatment

A multidisciplinary approach is required for these people including representation from pain clinics and/or appropriate medical practitioners in drug and alcohol services.

LINK
Chronic pain in 2.6.10

Pain management is important for people on substitution treatment with a terminal illness. Collaboration with palliative care and specialist services is most likely to achieve the integrated care needed |C|.

A7.7 Smoking cessation

LINK
Smoking cessation treatment in 2.6.7

Interventions for smoking cessation in the general population are also appropriate for patients being treated with substitution treatment for opioid dependence, although opioid dependent people may need more intensive treatment. The prevalence of smoking is higher amongst the population of opioid users than in the general population and many patients find it particularly difficult to overcome. However, the long-term adverse health effects of smoking make intervention desirable. Smoking cessation should be discussed with the patient towards the start of treatment, and revisited regularly |C|.

Consumer information and perspective

Legally competent patients have a common law right to make their own decisions about medical treatment and a right to grant, withhold or withdraw consent before or during treatment.

The following principles should apply:

- The free and informed consent of each patient to undertake treatment should be obtained in writing before treatment begins.
- Full disclosure of consumer rights and responsibilities, and the clinician's role and responsibilities, should occur at the commencement of treatment.

Patients should be given information on all aspects of treatment and their rights and responsibilities, including:

- the costs of treatment;
- frequency of appointments;
- availability of support services;
- an overview of policies and procedures of the treatment program;
- procedures for protecting patients' personal information (and in particular circumstances in which services may be obliged to disclose information);
- mechanisms for resolving grievances between patients and those responsible for their treatment;
- the nature of the treatment;
- any potential hazards and problems such as risks of overdose and impaired ability to drive if other depressants are combined with methadone or buprenorphine;
- risks associated with ceasing treatment;
- information about other relevant health issues e.g. pregnancy and breastfeeding, HIV, hepatitis C;
- information about safe procedures for storing pharmacotherapies, particularly out of reach of children;
- alternative treatment options.

Written information should be provided to each patient in a form that the patient can take away. Patients who cannot read should be read their rights and obligations at the time they enter the program. A competent interpreter should be used for patients who are not fluent in English, and where possible, information should be available in other languages.

People whose mental state impairs their capacity to provide informed consent (e.g. those with an acute psychotic illness, or a severe affective disorder) should receive adequate treatment for the psychiatric condition so that informed consent can be obtained before initiation of substitution treatment.

A8 Consumer information and perspective

In providing information to potential patients, there needs to be a balance between ensuring appropriate informed consent, whilst avoiding overwhelming the person and making this step a deterrent to treatment engagement. Information provision should be repeated at intervals throughout treatment. Note that renewal of consent at specified intervals may be a jurisdictional requirement. The nature of the information provided and the engagement of the patient in the decision-making process is likely to change as treatment progresses.

The prescriber and dispenser and other members of the therapeutic team have a duty of care to the patient that may necessitate sharing of information but this needs to be balanced with patient rights to maintain confidentiality. Legal provisions for disclosure of personal information to lessen or prevent threat to the individual or a serious threat to public health and safety are also relevant considerations.

Clinicians will need to communicate with pharmacists and other healthcare providers about opioid substitution treatment of individual patients (e.g., to verify a prescription). Signed patient consent to such disclosures must be obtained before individually identifiable addiction treatment information is provided to any third party (and patients can insist on their information not being shared).

Clinicians should be aware of jurisdictional requirements concerning privacy and confidentiality, and safeguards regarding access with electronic prescribing. Clinicians and patients should be made aware that, in some jurisdictions, if an opioid prescriber suspects that a child is at risk of significant harm, client confidentiality will no longer apply as the prescriber is then legally required to notify the relevant child protection agency and will need to inform the patient of their legal requirement.

Good clinical practice

A9.1 Linkages between prescriber, dispenser and adjunct services

LINK
3.4 Case management or care coordination

The relationship between the prescriber and dispenser of medication for substitution treatment requires ongoing communication to ensure consistency in the overall treatment program. This communication can be facilitated by the development of coordinated care plans.

A9.2 Response to administration of incorrect dose of medication

In the case of an accidental overdose with methadone, the critical issues which determine how clinicians should respond are the patient's level of tolerance and the amount of methadone given in error.

- Patients in the first two weeks who receive a dose that is higher than prescribed, of any magnitude, require observation for four hours. If signs of intoxication continue, more prolonged observation is required. This may involve sending the patient to an Emergency Department.
- Patients who have been on a methadone dose greater than 40mg/day consistently for two months will generally tolerate a dose double their usual dose, without significant symptoms. For a dose that is greater than double the usual daily dose the patient will require observation for at least four hours. If signs of intoxication are observed, more prolonged observation must be maintained.
- If patients are receiving regular take-away doses, or if they do not attend daily, it cannot safely be assumed that they have been taking their daily dose and have an expected level of tolerance. Therefore, such patients require observation in the event of a dose that is more than 50% of their usual dose.
- Patients in whom the level of tolerance is uncertain (dose <40mg/day, or in treatment for <2 months) require observation for at least four hours if they are given a dose more than 50% higher than their usual dose.

In all cases of dosing error the following procedures should be followed:

- Doses up to 50% in excess of the normal dose:
  - Advise the patient of the mistake and carefully explain the possible consequences.
  - Inform the patient about signs and symptoms of overdose and advise him/her to go to a hospital Emergency Department if any symptoms develop.
  - The dispenser must advise the prescribing doctor of the dosing error and record the event.
- Doses greater than 50% of the normal dose:
  - Advise the patient of the mistake and carefully explain the possible seriousness of the consequences.
  - The dispenser must contact the prescribing doctor immediately. If the prescriber is unable to be contacted consult a drug and alcohol medical specialist.

A9 Good clinical practice

  - If it is decided by the prescriber or addiction medicine specialist that the patient requires hospitalisation, the reasons should be explained to the patient and they should be accompanied to the hospital to ensure admitting staff receive clear information on the circumstances.
  - If the patient has left before the mistake is realised, every attempt should be made to contact the patient.
- Caution regarding inducing vomiting:
  - Inducing vomiting may be dangerous and is contraindicated if the patient has any signs of CNS depression.
  - Emesis after the first ten minutes is an unsatisfactory means of dealing with methadone overdose as it is impossible to determine if the entire dose has been eliminated.
  - In circumstances where medical help is not readily available or the patient refuses medical care, induction of vomiting (by mechanical stimulation of the pharynx) within 5-10 minutes of ingesting the dose may be appropriate as a first aid measure only. Ipecac syrup is contraindicated as its action may be delayed.

The risks associated with an incorrect dose of buprenorphine are not as severe as with full opioid agonist medications. In the event of an incorrect dose being administered:

1. The dispensing pharmacist (or nursing staff) should immediately notify the patient and the prescriber of the error.
2. The patient should be warned of the likely consequences (increased sedation or drowsiness may occur for several hours afterwards), and warned against any additional drug use, and driving or operating machinery, for the rest of the day.
3. If a higher than intended dose has been taken and any of the following circumstances apply, the patient should be monitored for at least six hours by trained health professionals or in the Emergency Department of a hospital:
   (a) the patient is sedated following the dose (for any reason);
   (b) the patient is new to substitution treatment (within the first two weeks); or
   (c) a buprenorphine dose of 64mg or greater was incorrectly administered (regardless of routine daily dose).

The patient should be reviewed by the prescribing medical officer prior to the next dose of buprenorphine. It may be that a lower dose, or no dose, is required the following day (in effects, a two-day dose has been administered).

Jurisdictional issues

A10.1 Patient transfers

LINK
Appendix 11: Further reading and resources

The transfer of people receiving methadone or buprenorphine treatment from one Australian jurisdiction to another should be arranged in accordance with the policies and procedures of each jurisdictional authority. Under usual circumstances transfer should not occur until arrangements have been finalised and this can take up to four weeks. A letter containing the following details should arrive at the new destination, prior to the arrival of the individual:

- identifying information (including photograph);
- methadone or buprenorphine dose;
- contact details of previous dosing point;
- exact dates of transfer;
- details of any takeaway doses provided; and
- relevant clinical information as required by each jurisdiction.

A10.2 Travelling overseas with methadone, buprenorphine or naltrexone

Medications used in the treatment of opioid dependence should not be transported across international borders unless they are accompanied by a customs clearance from the country concerned.

See http://www.tga.gov/au/consumers/travellers-leaving.htm

Jurisdictional requirements for the provision of takeaway doses for the purposes of travel also need to be considered.

It is strongly recommended where approval is given for takeaway doses that the embassy or consulate of all the countries to be visited be contacted to confirm any special requirements for personal importation of methadone or buprenorphine (e.g. number of doses permitted). Usually a doctor's prescription or letter will be adequate to present to Customs to confirm that the drugs are required for the treatment of a medical condition and possession is in accordance with Australian laws. However, if the overseas authorities require a letter from the Australian Government, this must be obtained from the Therapeutic Goods Administration (TGA).

http://www.indro-online.de/travel.htm is the best site for information on travelling overseas with methadone or buprenorphine.

As with other Schedule 4 drugs it is recommended that people using naltrexone obtain a letter from their doctor to present to Customs. The letter should state that the drug is required for the treatment of a medical condition. It is also recommended that the embassy or consulate of all the countries to be visited be contacted to confirm if the drug is permitted in their country.

A10 Jurisdictional issues

A10.3 Authorisation, training and support of prescribers and dispensers

Jurisdictions should have mechanisms in place to monitor and continually improve the quality of pharmacotherapy treatment. These mechanisms should ensure that specialist services are engaged in prescriber accreditation or formal quality improvement programs.

All service providers contributing to the treatment of opioid dependence should receive adequate orientation, training, support and supervision. This includes nurses, pharmacists and counsellors.

Doctors should not prescribe substitute medication, such as methadone or buprenorphine, as an isolated treatment modality. A multidisciplinary approach to drug treatment is essential. Prescribing should be seen as an enhancement to other psychological, social and medical interventions.

A doctor prescribing controlled drugs for the management of drug dependence should have an understanding of the basic pharmacology, toxicology and clinical indications for the use of the drug, dose regimen and therapeutic monitoring strategy.

Jurisdictions should develop professional training programs for prescribers intending to prescribe methadone and buprenorphine and assess the competence of medical practitioners wishing to be approved as prescribers.

LINK

Appendix 11: Further reading and resources

Methadone and buprenorphine are registered Schedule 8 medications. Each jurisdiction is responsible for a system for authorising medical practitioners to prescribe methadone or buprenorphine for the purpose of treating addiction. Check your jurisdictional policy for details of authorisation procedures.

A medical practitioner intending to prescribe pharmacotherapies for the treatment of opioid dependence should have knowledge and skills in the assessment and treatment of drug dependence.

The number of patients that doctors are approved to treat should be determined by:

- the expertise and experience of the doctor in treating drug dependence;
- the accessibility of the doctor to the individual;
- whether the doctor is working full-time or part-time in the treatment of opioid dependence; and
- the type of patients and type of setting in which the doctor is providing treatment, including for example, the availability of other clinicians and ancillary services.

It is appropriate for limits on the number of patients to be varied according to the expertise of the prescriber and the available professional support. There is some variability between jurisdictions in these limits, and also the processes of approval. Refer to the relevant jurisdictional authority for detailed information.

A10 Jurisdictional issues

The dispenser is legally required to assess whether a dose of medication is appropriate and can withhold treatment if necessary.

Limits may be placed on the number of patients able to receive methadone or buprenorphine at particular dispensing locations. Such limits are likely to vary according to the capacity of the dispensing point and the experience of staff, as well as circumstances in the particular locality. Refer to the relevant jurisdictional authority for detailed information.

LINK

Appendix 11: Further reading and resources

A10.4 Criteria for takeaways and unsupervised dosing

The evidence base on takeaway doses is very limited with most studies of substitution treatment occurring in the context of supervised dosing.

LINK

Takeaways and unsupervised dosing in A4.3.1

2.3.6 Maintenance doses

Glossary of terms

Policies on supervised administration of medications and provision of takeaway doses need to strike a balance between recognition of patients' rights to autonomy, practitioners' duty of care, child protection, and public concerns about diversion of medication.

In addition to supervised administration, and procedures for approval of takeaway doses, specific strategies that can be used to manage the risks include dilution of takeaway doses of methadone and the use of film rather than tablet preparations of buprenorphine.

Diluting takeaway doses of methadone reduces the chance of an entire dose being accidentally swallowed, for example by a child, it discourages injection, and reduces the value of diverted methadone. It is recommended that doses greater than 25mg are diluted to 100ml, while smaller doses can be diluted to 50ml (depending on jurisdictional guidelines, which may specify dilution volumes). The Biodone Forte brand of methadone may be diluted with purified water, but methadone syrup should be diluted with a preservative solution. This enables takeaway doses to be kept in a cupboard and not in a refrigerator where they may be mistaken as a drink and accessed by children.

The film preparation of buprenorphine-naloxone adheres more tightly to the mucosa of the mouth compared to tablet preparations and hence is more difficult to divert.

The extent to which takeaway doses and unsupervised dosing is possible is determined by State and Territory government regulations with specific policies established by jurisdictional guidelines.

Assessment of the suitability of individual patients for takeaway doses is the responsibility of the prescriber, and requires consultation with dispensing staff, regular review of the patient and assessment of their substance use, medical and social circumstances, reasons for takeaways, and the safety of others, particularly children. Assessment should include capacity to comply with jurisdictional requirements regarding safe storage of takeaway doses. Prescribers should ascertain whether a patient has children in their care (especially children under five years) before authorising takeaway doses. The prescriber must document dosing conditions (number of takeaways, unsupervised dosing) on the prescription.

A10 Jurisdictional issues

In the context of substitution treatment of opioid dependence, criteria that are indicative of low risk with regards to takeaway doses are:

- regular attendance at appointments;
- urine samples provided for screening when requested;
- no or infrequent use of additional opioids;
- no use of benzodiazepines, or prescribed use is at low levels and stable;
- alcohol consumption is not at hazardous levels;
- no use of illicit stimulants;
- no evidence of recent (e.g. in prior 3 months) intoxicated presentations or overdoses;
- recent pattern of medication use has been in accordance with prescription (no missed doses).

It is important that clinicians consider the balance of potential benefits and risks each time they authorise takeaway doses.

In this context several patterns of takeaway dosing are possible (but the acceptability of these patterns will depend on system support and policies within each jurisdiction):

(1) Dosing is primarily supervised but takeaways may be approved for one day at a time due to the dispensing point not being open 7 days a week, or family, work or study commitments, or ill health making patient attendance at the dosing point difficult. In approving single occasion takeaways, prescribers should place emphasis on the safety of the patient and their family.

(2) Partially supervised dosing where a combination of supervised and takeaway doses is routinely provided. Patients may receive up to six takeaway doses per week, with the number of consecutive days determined by jurisdictional regulations. Phased introduction of more takeaways is appropriate, where deemed to be clinically safe, and the number of takeaway doses per week should be based on assessment of the circumstances of the individual and monitoring of the response to takeaway dosing. A pattern of dosing with more than four takeaways per week would usually be permitted only for buprenorphine-naloxone, with methadone considered less suitable due to the greater risk of inappropriate use and overdose in patients and others. This pattern of dosing is only suitable where the benefits to the patient are considered to outweigh the risks. The possibility of dosing being supervised by a responsible adult away from the dispensing point may also be a consideration.

(3) Unsupervised dosing where medication is dispensed without regular or frequent (i.e. less than weekly) supervision of dosing. Such arrangements would be suitable for long-term stable patients who are unable to maintain stability without medication-assisted treatment, and should be restricted to treatment with buprenorphine-naloxone. This dosing arrangement is only available in some jurisdictions.

For all three patterns of takeaway dosing, prescribers should regularly (minimum of every three months) assess the suitability of patients for takeaway doses, and document the assessment in the patient's records.

Given the limited evidence base on takeaways and unsupervised dosing, further evaluation of patient outcomes and unintended adverse impacts related to the pattern of takeaway dosing is highly desirable.

National Guidelines for
Medication-Assisted Treatment
of Opioid Dependence

PART B

Supporting information

1 Supporting Information

Context for the guidelines

1.1 Opioid use in Australia

1.1.1 Patterns of use

The prevalence of opioid use and dependence in Australia remains low. The 2010 National Drug Strategy Household Survey[11] found that 1.4% of people in Australia aged 14 years or older had used heroin in their lifetime and 0.2% in the previous 12 months. Between 2001 and 2010 there was no significant change in the proportion of people using heroin in Australia.

For those participants in the 2010 National Drug Strategy Household Survey who reported recent heroin use, 63.2% reported use at least once a month. Recent heroin use was highest among those aged 30-39 years.

Heroin continues to be the drug of choice for the majority of injecting drug users. Of the injecting drug users who participated in the Illicit Drug Reporting System in 2012[12], 54% identified heroin as their drug of choice but with substantial variation, with speed or methamphetamine being the most common drug of choice in Tasmania, while morphine was most common in the Northern Territory.

There is an increasing population of patients who develop harms related to their use of pharmaceutical (prescription and over-the-counter) opioids for medical conditions – usually in the context of chronic pain. The marked increase in the prescription of opioid medication in Australia over the past 20 years is resulting in increasing numbers of patients who develop pharmaceutical opioid dependence, and require assistance in the management of dependence in addition to any concomitant medical conditions.

1.1.2 Consequences of unsanctioned opioid use

The health, social and economic costs to the individual and community associated with illegal drug use, including opioids, are substantial and derive from:

- premature mortality;
- reduced quality of life and productivity;
- drug related crime.

Dependent opioid users are at most risk of overdose and other health harms, and are most likely to be criminally active.

[11] Australian Institute of Health and Welfare 2011. *2010 National Drug Strategy Household Survey report.* Drug statistics series no 25. Cat. No. PHE 145. Canberra: AIHW. www.aihw.gov.au. Accessed 4 April 2012.

[12] Stafford J & Burns L (2013). *Australian Drug Trends 2012. Findings from the Illicit Drug Reporting System (IDRS).* Australian Drug Trends Series No. 91. Sydney, National Drug and Alcohol Research Centre, University of New South Wales. ndarc.med.nsw.edu.au

1 Context for the guidelines

Mortality

Globally, opioids make the largest contribution to illicit drug-related death. Estimates of annual mortality rates for opioid users typically range between one and three per cent (Darke, Mills, Ross, & Teesson, 2011). The major causes of death are overdose, disease (predominantly AIDS), suicide and trauma. In countries with a high prevalence of HIV amongst injecting drug users AIDS is a major cause of death, while in countries with a low prevalence of HIV overdose, suicide and trauma play far greater roles (Darke, et al., 2011).

Deaths amongst opioid users generally occur at a younger age, relative to mortality related to alcohol or tobacco. The average age at death for a cohort of opioid users in the Australian Treatment Outcome Study was 34.5 years (Darke, et al., 2011). In this cohort the mortality rate was four and a half times the expected population rate and overdose was overwhelmingly the major cause of death.

Crime

The relationship between illicit drugs and crime is complex. There are no necessary or inevitable causal links between licit and illicit drugs and crime. Most drug users are not otherwise involved in criminal activity, and there is little evidence that drug use, in and of itself, causes people to commit crimes, or that criminal activity in and of itself, causes people to use drugs. Nonetheless drugs do play an important role in violent and property crime (W. Hall, 1996; Jan Keene, 2005).

The association appears particularly strong for illicit drug use and property crime (robbery; break, enter and steal; forgery; shoplifting). One estimate is that the extent of involvement in property crime among people who are drug dependent is about 10 times higher than among non-users (Egli, Pina, Christensen, Aebi, & Killias, 2009)

Blood-borne virus infections

The potential for epidemic spread of blood-borne viruses through sharing of contaminated needles, syringes and other injecting equipment is high. Since sharing or use of contaminated syringes and needles is a very efficient way of spreading HIV, it can spread very rapidly amongst injecting drug users (Des Jarlais, Friedman, Woods, & Milliken, 1992; Stimson, 1995).

It is not only the spread of HIV/AIDS amongst people who inject drugs that is relevant. People who inject drugs who become infected with HIV can become a means of transmission to the general population through relationships with people who are not drug users, as well as transmission to unborn children by infected mothers. Links between drug use and commercial sex work are also significant to the spread of HIV

1 Context for the guidelines

beyond the population of people who inject drugs. Indeed UNAIDS reports that the HIV epidemic is evolving. In Eastern Europe and Central Asia, epidemics that were once characterized primarily by transmission among injecting drug users are now increasingly characterized by significant sexual transmission, including in parts of Asia, transmission among heterosexual couples (UNAIDS, 2010).

The prevalence of HIV infection amongst people who inject drugs in Australia remains low [less than 2%], but the proximity of Australia to countries in the South-East Asian region with a much higher prevalence of HIV means that there remains a risk of an epidemic of HIV infection occurring in Australia. Ongoing vigilance is important.

The hepatitis C virus (HCV) is more robust than HIV and more easily spread and consequently is much more prevalent than HIV. Unsafe injection practices are the main route of transmission, accounting for an estimated 90% of new hepatitis C infections. Between 25% and 40% of people will clear acute hepatitis C, with the chronic infection persisting in the majority. Current estimates are that around 7% of untreated, chronic HCV carriers will develop liver cirrhosis within 20 years[13]. The large number of people infected and the more protracted complications will result in the health and medical cost of HCV transmitted by injecting drug use being considerably greater than that of HIV. Hepatitis C infection is well established amongst people who inject drugs in Australia indicating a significant source of morbidity in this population.

Depending on viral genotype and other cofactors, 30-70% of patients have a sustained response to currently approved treatments for hepatitis C[14]. An important aspect of the treatment of opioid dependence is addressing hepatitis C treatment, usually by encouraging referral to specialist services.

LINK
Hepatitis C in 2.6.8

1.2 Treatment response

1.2.1 Goals of treatment

Most people taking action to modify their drug use behaviour do not successfully maintain their gains on their first attempt. With tobacco smoking, for example, successful self-changers make an average of three to four attempts before they become long-term abstainers. Relapses occur frequently. Follow-up studies indicate a similar pattern for opioid drugs. People who are dependent may continue to use opioids for decades. Among these users, periods of daily use are interrupted by detoxification, drug treatment and incarceration for drug-related offences. It is this pattern of use, cessation and relapse that causes opioid dependence to be regarded as a chronic relapsing condition (McLellan, Lewis, O'Brien, & Kleber, 2000).

The proportion who achieve enduring abstinence from opioid drugs after any treatment encounter is small but it increases with time and age (Gossop, 2011). The Australian Treatment Outcome Study followed three cohorts of heroin users from the time of entry to treatment (opioid substitution treatment with methadone or buprenorphine,

[13] *HIV, viral hepatitis and STIs: A guide for primary care*. Australasian Society for HIV Medicine (2008). Available from http://www.ashm.org.au. Accessed 9 April 2013.

[14] ibid

1 Context for the guidelines

detoxification, or residential rehabilitation) and a comparison group of heroin users who were not in treatment when they were recruited to the study. Over a three year period 99.3% of study participants had been exposed to some form of treatment (including 92.9% of the "no treatment" comparison group). At baseline 99% reported using heroin in the month prior to interview, compared to 35% at 24-month and 36-month follow-up interviews. One month abstinence from heroin was associated with having spent more time in opioid substitution treatment and residential rehabilitation, but was unrelated to time spent in detoxification (Teesson et al., 2008).

A more detailed and longer-term perspective on the response to opioid substitution treatment is provided by a study from the USA. In the late 1970s, a cohort of dependent heroin users was recruited from a methadone maintenance treatment program in California. Successive research teams have followed this cohort over 30 years. Nearly half of the original sample were deceased at the 30-year follow-up, but amongst the survivors four distinct patterns of response to treatment were identified (Grella & Lovinger, 2011):

- about 25% decreased their heroin use relatively rapidly and quit altogether over 10 to 20 years;
- 15% achieved a more moderate decrease in their heroin use but also quit over 10 to 20 years;
- 25% achieved a gradual decrease in heroin use over the 30 years of follow-up and
- 25% did not reduce their heroin use at all and were still using at the 30-year follow-up.

The broad goal of treatment for opioid dependence is to reduce the health, social and economic harms to individuals and the community arising from unsanctioned opioid use.

The community expectation of "treatment" of drug dependence is, in general, that it will result in drug users achieving a drug-free lifestyle. Abstinence is an important long-term goal, but this viewpoint of treatment does not adequately reflect the complexities of drug dependence, or the extended treatment period required by some people.

An emphasis on abstinence to some extent devalues the other achievements that can be made through treatment. For most people entering treatment, short-term achievable goals are important, such as:

- staying alive;
- reducing unsanctioned drug use;
- reducing risk of infectious disease;
- improving physical and psychological health;
- reducing criminal behaviour;
- reintegration in the labour and educational process; and
- improving social functioning

without necessarily ceasing drug use.

1 Context for the guidelines

These goals represent steps along a continuum, extending from chaotic drug use, to reduced, safer use, through to abstinence. Reduced or controlled use, stable relationships, employment or better health are all important changes that may encourage abstinence in the future.

'Slip ups' or lapses are a normal part of changing any human behaviour. Every time they occur, a person can learn from the experience and develop better ways of dealing with a similar situation in the future. It may be only through a number of unsuccessful attempts at controlled use that a person decides on a goal of abstinence.

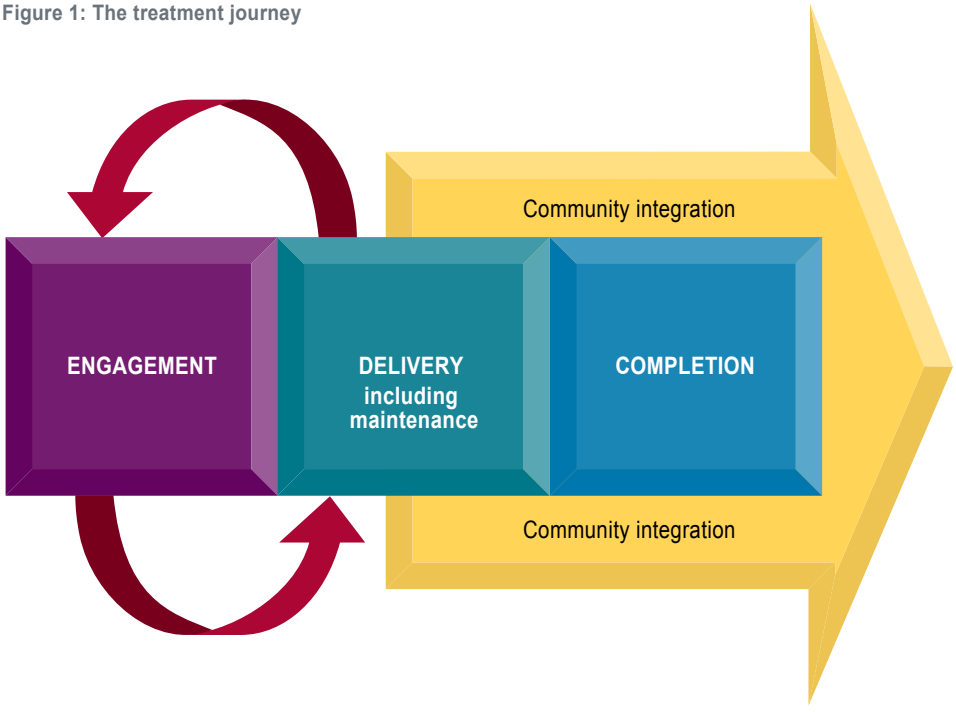
1.2.2 Patient perspective: the treatment journey

Dependent alcohol and other drug users may express a strong desire to be abstinent but remain ambivalent about treatment and about ceasing use. As the negative consequences of alcohol and drug dependence escalate, the individual becomes increasingly conflicted about continuing use (Fiorentine & Hillhouse, 2000). This conflict will move some individuals to contemplate and take action to change their behaviour.

The chronic relapsing nature of drug dependence, and individual variability in personal circumstance indicates a need for services that are sufficiently varied and flexible to respond to the needs of patients, their severity of dependence, personal circumstance, motivation and response to interventions, and that will support their progression through the different stages of behavioural change (L. Gowing, Proudfoot, Henry-Edwards, & Teesson, 2001).

As treatment progresses, patient needs change making it necessary to continually assess and modify an individual's treatment and services plan. Furthermore, treatment journeys are not linear, but there is progression through stages with relapses common.

Figure 1: The treatment journey



1 Context for the guidelines

There is no ‘best method’. No one type of treatment will work for everyone. Individuals seeking treatment for drug dependence will have different patterns of risk and protective factors, different psychological and social problems, and varying cultural backgrounds. People may need to try a number of options before finding what best suits them. Also, a certain type of treatment may suit a person at one stage in their life, but may not be useful at another.

Facilitating patient choice by providing a range of treatment options is an important influence on the decision to enter and stay in treatment and on compliance with treatment. Retention in treatment is in turn associated with benefits in terms of reduced drug use, reduced criminal activity, and improved health and social well-being.

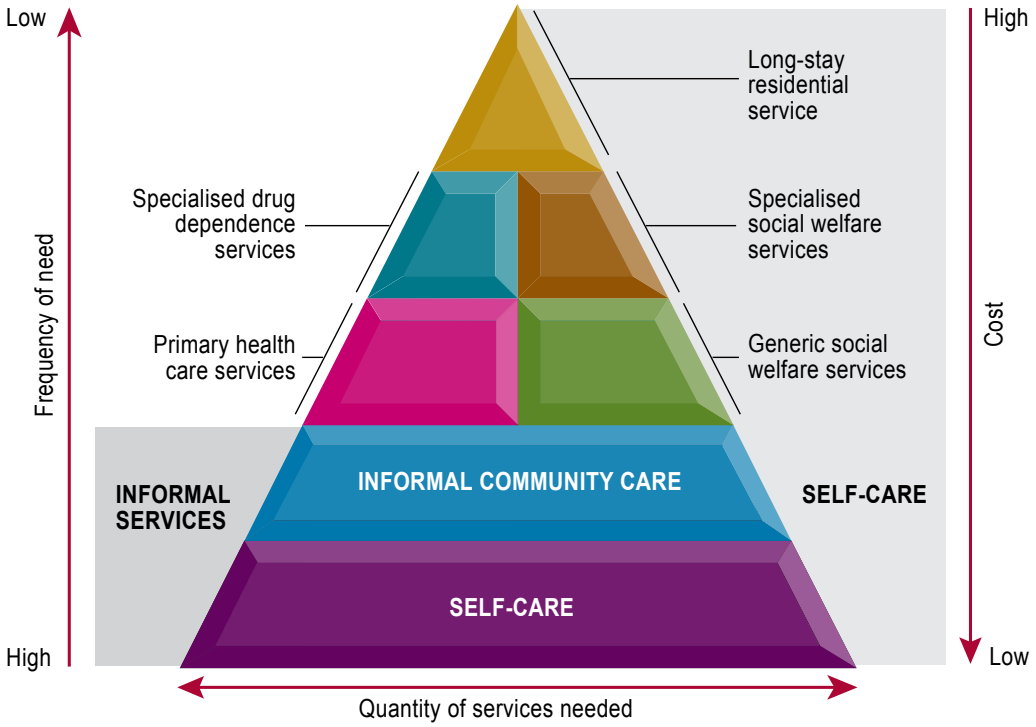
Drug users commonly present for treatment at a time when they are in crisis. It may be that their opioid use has escalated to a point of being out of control, or, sometimes, a change in their circumstances, such as an ultimatum from family, or being charged with a criminal offence, may be the precipitant to entering treatment. In these crisis situations there is often a resolve to cease drug use and change their lifestyle, but they often seek short-term treatment, without necessarily having considered all their treatment options, simply ‘hoping’ that an attempt at withdrawal will be sufficient to stop heroin use. A treatment system able to respond effectively to opioid use is one that provides a range of options, at least some of which can be accessed quickly and with multiple points and levels of entry.

Clinical experience and research have repeatedly demonstrated that motivation to remain abstinent is often short-lived. There is strong evidence that longer-term treatment is associated with a greater likelihood of long-term abstinence than are shorter periods of treatment. Stability and consequent improvements in drug use and psychosocial stability gained as a result of opioid substitution treatment tend to become significant after three months of treatment, or more, with the majority of benefit gained after one year (benefits may be sustained beyond this point with continued treatment). However, this is seldom what patients or their families wish to hear at the time of entering treatment.

The concept of stepped care is relevant, meaning initiation at a low level of intervention with the intensity escalating depending on the individual’s response to the first level, and stepped down care in response to progress. An individual may require varying combinations of services and treatment components during the course of treatment and recovery.

1 Context for the guidelines

Figure 2: Service organisation pyramid for optimal mix of services for alcohol and other drug users



1.2.3 *Importance of integration*

A comprehensive alcohol and other drug treatment system requires input from both specialist and generalist service providers (Figure 2). This type of integrated system involves strong primary health care which opens access to services such as brief assessments and brief interventions. These open access services then support more structured interventions for alcohol and other drug use. This conceptual approach also envisages the integration of systems across the health and human services sector to meet the various needs of alcohol and other drug users that are important to recovery.

A systematic planned treatment system provides greater opportunity for linkages between specialist and generalist services and a more structured approach to service delivery. A planned treatment system will be easier for both patients and service providers to navigate to ensure optimal treatment outcomes for patients. Achieving this sort of framework requires that primary health care providers, and the health and human services sector in general, have a good awareness of alcohol and other drug issues. This in turn necessitates that alcohol and other drug issues are incorporated into training programs for a broad range of professions.

Drug use can be a very complex problem, interlinked with many other problems, including social exclusion. Linkages to education, employment and welfare agencies, as well as to the criminal justice system, are important components of the system (UNODC, 2003). In the long-term, there is a need for help in the process of social inclusion. Lengthy involvement in crime and drug use reduces opportunities to engage in 'normal' life, including relationships, employment or accommodation (J. Keene, Stenner, Connor, & Fenley, 2007). Therefore it is important that the treatment system is holistic and brings key local agencies into working partnerships in order to maximise the overall effectiveness of the service response (UNODC, 2003).

1 Context for the guidelines

Drug treatment systems should be well integrated with other systems of care and social support, to provide opportunities for patients of alcohol and other drug treatment services to receive appropriate housing, social support, education and employment to maximise treatment gains and enable reintegration into local communities (National Treatment Agency for Substance Misuse, 2006).

The severity of dependence, the nature and extent of psychiatric comorbidity, and the nature and stability of social circumstances are all important dimensions in determining the most appropriate type and intensity of treatment. It is imperative that the treatment system is responsive to individual needs and recognises the rights of patients to choose preferred treatment options and be active in all decision making processes regarding their treatment.

Patients may require the provision of several different types of treatment service over time (that is, a continuum of care). It is quite common for an individual receiving treatment from one provider to receive additional welfare support and other social inclusion services provided by other agencies. It is also frequent that treatment services provided by different agencies are provided in sequence, such as detoxification, residential care and outpatient counselling (UNODC, 2003).

There may be quite complex referral and assessment decision-making processes that operate when individuals are patients of the alcohol and other drug treatment system. Assessment and appropriate placement of a patient within the system is crucial and will be influenced by immediate needs and those emerging over the course of a treatment episode and aftercare (UNODC, 2003). For patients who wish to be drug-free, treatment systems need to be configured to create planned exits from treatment, including drug-related aftercare and support (UNODC, 2003).

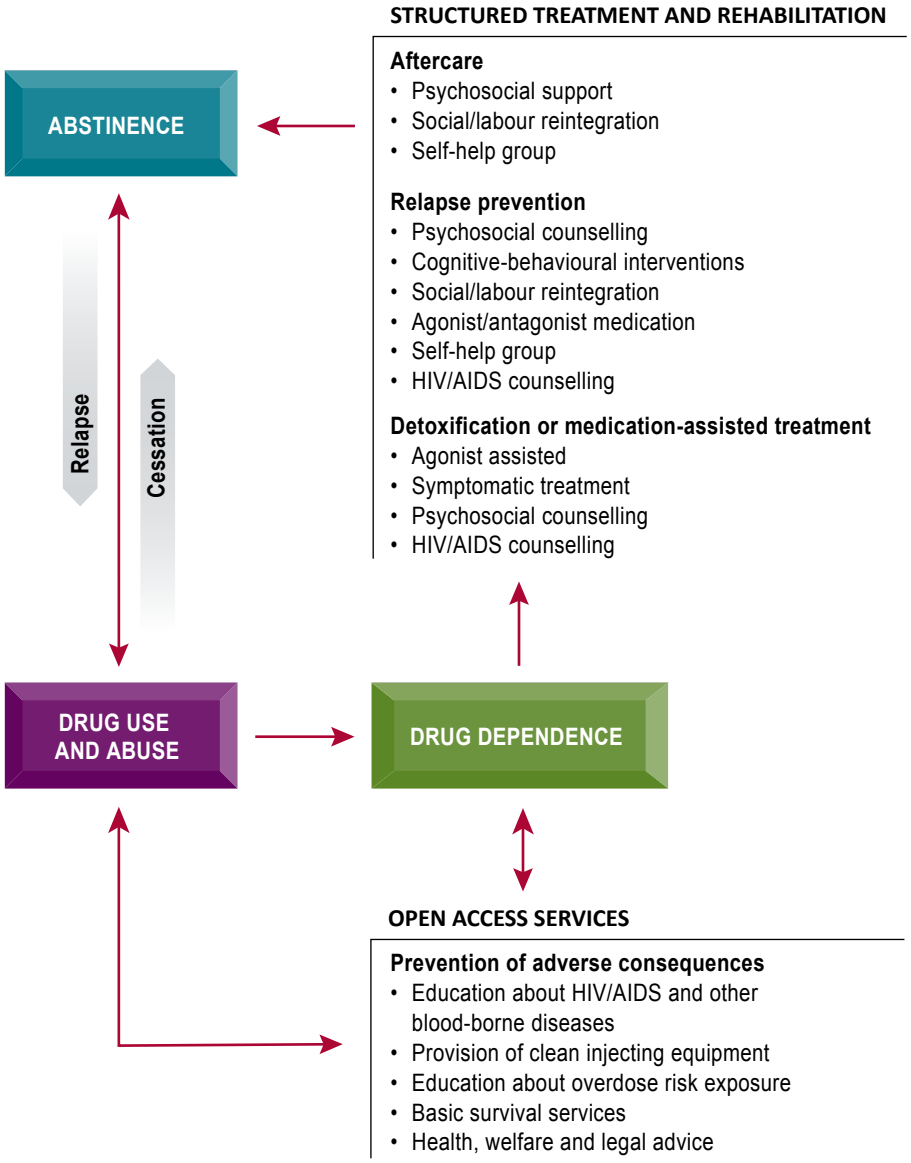
Streamlined referral processes and communication between services are desirable. A mix of sequential, parallel and integrated approaches to treatment would bring together, for the benefit of the service user, the sensible and practical elements of drug and mental health systems, for example, while continuing to recognise the differences and specialist elements of each sector (Holt, Treloar, McMillan, Schultz, & Bath, 2007).

1 Context for the guidelines

1.2.4 *Types of treatment*

Figure 3 represents the broad range of treatment options, related to the stage of dependency. The nature of these options is outlined briefly below.

Figure 3: Types of treatment and pathways



1 Context for the guidelines

Screening and brief intervention

Drug users are often reluctant to enter treatment. They may lack insight into the negative consequences of their use of drugs, and they may be in a state of denial about their level of use. Contact with primary health care services, police, the criminal justice system, and outreach activities provide opportunities for the delivery of brief interventions to this group of users.

Brief interventions are structured therapy of a limited number of sessions, usually one to four (UNODC, 2003), sometimes requiring no more than five minutes, and sometimes up to two hours in total. Such interventions can provide information about drug use, particularly through approaches to reduce the risks of drug use, both to the individual and the general community. Brief interventions also aim to increase awareness of the negative aspects of drug use and reasons for ceasing use, to motivate users to take action to modify their drug using behaviour, and to encourage them to engage in treatment.

Brief interventions on their own can promote behavioural change, particularly for people whose drug and alcohol use is at levels associated with low to moderate risk of harm (Dunn, Deroo, & Rivara, 2001; McCambridge & Strang, 2004), or can be the first stage of more intense treatment. Brief interventions are appropriate for individuals from a wide range of cultures and backgrounds (Rachel Humeniuk et al., 2012) and can be used in a variety of settings, both opportunistic and within specialised drug and alcohol treatment.

Open access services are important components of this level of intervention and encompass “drop-in”, community outreach, telephone helplines, support groups and general support services. These services can encourage individuals to take action to reduce their drug use without formal treatment, they can provide interventions such as clean needle and peer education programs to reduce the harms of drug use and the risk of overdose, and they can act as entry points to more formal treatment approaches.

Detoxification

Chronic use of alcohol and other drugs is associated with physiological changes that comprise physical dependence. Users who are dependent must undergo detoxification if they are to become abstinent.

Withdrawal occurs when the drug of dependence is eliminated from the body, and any physical adaptation that has occurred as a consequence of dependent drug use is reversed. The nature and severity of withdrawal depends on an individual’s drug use history and the pharmacology of drugs used.

People may experience withdrawal in a variety of settings, including general hospitals, specialist drug and alcohol units, outpatient and home. Detoxification entails the provision of interventions to ensure that the withdrawal process is completed with safety and minimal discomfort. Many drug users cease use without assistance from detoxification services; others may be supported by family members or other services.

1 Context for the guidelines

Because detoxification addresses only the physical adaptation, and not the social dimension of dependence, detoxification is not in itself a treatment for dependence. Rather, detoxification is a necessary stepping stone to drug-free treatment.

Rates of relapse following detoxification tend to be high. Given that tolerance is reduced by detoxification, there is also a high risk of overdose associated with relapse in the period after detoxification. Nonetheless, detoxification provides a limited opportunity for interventions which may encourage users to move towards the next stage of change, and at least a period of respite from the risks associated with regular use of alcohol and other drugs as well as promoting engagement in further treatment.

Substitution treatment (agonist maintenance)

Substitution treatment involves the prescription of a drug with similar properties to the drug of dependence, but with a lower degree of risk. The value of substitution treatment lies in the opportunity it provides for dependent drug users to reduce their exposure to risk behaviours and stabilise in health and social functioning before dealing with the physical dimension of dependence.

The main forms of substitution treatment are prescribed methadone or buprenorphine for opioid dependence and nicotine replacement therapy (patches, gum, inhalers) for tobacco smoking. Psychosocial support, at various levels, is an integral part of opioid substitution treatment.

Methadone maintenance treatment (MMT) was first endorsed by State, Territory and Commonwealth Governments as an appropriate and useful treatment for heroin dependence at the launch of the National Campaign Against Drug Abuse (now the National Drug Strategy) in 1985. The availability of treatment services for drug users remains integral to the National Drug Strategic Framework. It is recognised that the provision of treatment services for people who are drug dependent reduces drug use and prevents drug-related harm.

At June 2011 there were 46,446 patients (65% male) receiving opioid substitution treatment from 1,444 prescribers in Australia[15]. From 1998 to 2011 the rate of participation in opioid substitution treatment doubled, from 1.3 patients per 1000 population in 1998 to 2.1 patients per 1000 population in 2011. Participation rates have been largely stable for three years, 2009 to 2011. The median age of patients was 38 years, with a trend of increasing age. In 2006, 72% were aged 30 years and over, compared to 85% in 2011. Methadone remains the medication most commonly prescribed. In 2011, 69% were receiving methadone, 14% buprenorphine and 17% buprenorphine-naloxone. (Note that NSW does not distinguish between buprenorphine and buprenorphine-naloxone – all are reported as buprenorphine which distorts these data somewhat.)

[15] Australian Institute of Health and Welfare, 2012. *National Opioid Pharmacotherapy Statistics Annual Data collection: 2011 report*. Cat. No. HSE 121. Canberra: AIHW. Available from www.aihw.gov.au. Accessed 13/12/12.

1 Context for the guidelines

Arrangements differ in each jurisdiction, but there has generally been an increasing reliance on the private sector for the provision of pharmacotherapy services in Australia. In 2011, 65% of patients received treatment from a private prescriber, 27% from a public prescriber, and 7% from a prescriber in a correctional facility.

Across Australia, the patient-to-prescriber ratio has remained relatively stable since 2005, in the range of 30 to 33 patients per prescriber, but with substantial variation depending on the prescriber type. In 2011, public prescribers had the highest ratio (61 patients per prescriber), followed by correctional facility prescribers (51 patients per prescriber) and private prescribers (26 patients per prescriber).

In 2011, there were 2,264 dosing point sites in Australia, an increase of 64 from 2009-10. Of these, 87.5% were located in pharmacies. The ratio of patients per dosing point site across Australia was 20.5 in 2011. A larger proportion of patients who received buprenorphine-naloxone were dosed at a pharmacy (84%) than those receiving methadone (69%) or buprenorphine only (55%).

Relapse prevention

Relapse prevention and rehabilitation programs are designed to change the behaviour of patients to enable them to regain control of their urge to use substances.

Counselling and psychosocial support, including self-help groups, are important components of relapse prevention approaches. Psychological interventions help patients to identify and address the reasons for drug use, the negative consequences of their drug use, and the benefits associated with changing drug user behaviour. Relapse prevention interventions comprise skills to recognise cues and risk factors for drug use, and the development of strategies to resist drug use.

Relapse prevention is an important component of opioid substitution treatment, and is integral to naltrexone treatment.

Living skills development

Problematic substance use is a complex condition combining social, psychological, behavioural and physiological dimensions. It is often a symptom of underlying social, psychological or behavioural issues which need to be addressed if recovery is to occur.

Psychological and social support interventions change drug using behaviour and address the various emotional issues, practical needs (housing, employment, financial management) and social interaction (family issues, building networks unrelated to drug use) for recovering drug users. Psychological treatment is also an important part of medicated treatment for supporting compliance with the prescribed treatment and minimising unsanctioned drug consumption. Concepts and definitions of recovery abound, but a consistent theme is recovery as a process, spanning years rather than weeks and months, and encompassing personal change, maximisation of health and well-being and participation in the rights, roles and responsibilities of society (Groshkova, Best, & White, 2013) . This understanding of recovery allows for several pathways, including through medication-assisted treatment (el-Guebaly, 2012).

1 Context for the guidelines

The aspects of recovery that are encompassed in the phrase “living skills development” are perceived as:

- requiring establishment or renewal of personal values, such as honesty, self-reliance, and responsibility to self and others;
- involving learning or re-establishing the behavioural skills, attitudes and values associated with community living; and
- involving personal development and lifestyle change consistent with shared community values.

This aspect of recovery is most commonly addressed through residential rehabilitation. Residential rehabilitation is based on the principle that a structured drug-free residential setting provides an appropriate context to address the underlying causes of addictive behaviour. These programs assist the patient to develop appropriate skills and attitudes to make positive changes towards a dependence-free lifestyle. Therapeutic communities represent a subset of residential rehabilitation defined by an emphasis on accepting personal responsibility for decisions and actions, and assigning residents tasks of “everyday living” as part of their treatment (Swindle, Peterson, Paradise, & Moos, 1995).

2 Supporting Information

Treatment approaches in Australia

Product and consumer information for medications on the register of therapeutic goods in Australia can be obtained from https://www.ebs.tga.gov.au/.

2.1 Medications: description and pharmacology

2.1.1 Methadone

Methadone was developed in Germany in 1941 for the relief of pain. It was used as a treatment for heroin dependence in Vancouver in 1959, in New York in 1964 and was introduced in Australia for the same purpose in 1969. Methadone is currently the most common pharmacotherapy used in Australia and is recognised nationally and internationally as an effective method for treating opioid dependence.

Methadone is a synthetic opioid agonist. In Australia the primary use of methadone is in substitution treatment but it may also be used as a withdrawal agent for those dependent on opioids. Methadone reduces the use of heroin and other opioid drugs through cross tolerance which results in a reduction of withdrawal symptoms, less desire to use other opioids, and reduced euphoric effects when opioid drugs are used. Methadone is taken orally on a daily basis.

Methadone is usually administered as an oral liquid (5mg/ml) for the treatment of dependence on opioid drugs. Methadone tablets and injections are also available but are generally used for analgesia and not for the treatment of opioid dependence.

Methadone therapeutically substitutes for other opioids and ameliorates problems because:

- the long half-life and a single daily dose of methadone produce a steady state which allows the person to function normally;
- methadone is orally active and slowly absorbed resulting in less intoxication and withdrawal symptoms.
- methadone is cross-tolerant with other opioid drugs allowing people who are opioid dependent to reduce drug-seeking, develop normal interests and pursue a more healthy and productive lifestyle.

Absorption and duration of action

Methadone is well absorbed after oral administration (mean bioavailability of around 75%). Methadone can be detected in the blood 15-45 minutes after oral administration, with peak plasma concentration at 2.5-4 hours (Eap, Buclin, & Baumann, 2002).

There is considerable variability in estimates of the elimination half-life of methadone (Eap, et al., 2002) with a mean value of around 22 hours, and with most values in the range of 20 to 36 hours (Eap, et al., 2002; R. Humeniuk, Ali, White, Hall, & Farrell, 2000). The prolonged half-life of methadone contributes to a continued rise in methadone blood levels during the first week of daily dosing, and a relatively slow fall in blood levels between doses.

2 Treatment approaches in Australia

An elimination half-life that is short may result in withdrawal. The consequences of this may be treatment failure and drop-out, or self-medication with other drugs and potential toxicity. Conversely, a very long half-life may indicate a greater blood methadone concentration for longer, and greater accumulation over a longer period, which may result in toxicity, particularly with multiple dosing.

Onset and duration of response to methadone	
Onset of effects	15-45 minutes
Peak clinical effects	2.5-4 hours
Duration of effects	20-36 hours

Methadone is highly bound to plasma proteins, in particular to α1-glycoprotein. Its mean free fraction is around 13%, with a 4-fold inter-individual variation (Eap, et al., 2002)

The is up to a 17-fold inter-individual variation of methadone blood concentration for a given dosage, with variations in metabolism accounting for a large part of this variation (Eap, et al., 2002).

Metabolism

Methadone is primarily broken down in the liver via the cytochrome P450 enzyme system with CYP 3A4 and, to a lesser extent, CYP 2D6 the main isoforms involved (Eap, et al., 2002). Approximately 10% of methadone administered orally is eliminated unchanged. The rest is metabolised and the (mainly inactive) metabolites are eliminated in the urine and faeces. Methadone is also secreted in sweat and saliva and, in small amounts, breast milk (Lauren M. Jansson et al., 2008).

LINK

2.6.3 Pregnancy and breastfeeding

Methadone reaches steady state in the body (where drug elimination equals the rate of drug administration) after a period equivalent to 4-5 half lives or approximately 3-10 days. Once stabilisation has been achieved, variations in blood concentration levels are relatively small and good suppression of withdrawal is achieved. As many as one-third of patients on methadone doses of 60mg/day may experience withdrawal symptoms in the latter part of the inter-dosing interval. A smaller volume of distribution, suggesting shortened terminal half-life, with greater binding to α1-acid glycoproteins may be a factor in this variability (Dyer, 2005). If dose increases or multiple dosing within a twenty-four hour period do not prevent withdrawal symptoms, transfer to buprenorphine should be considered.

Safety and side effects

The long-term side effects of methadone taken orally in controlled doses are relatively minor, although the effect of chronic opioid use on teeth, constipation, sexuality and sleep can cause considerable distress and need to be managed. Central sleep apnoea can also be a complication of methadone treatment (Teichtahl, Prodromidis, Miller, Cherry, & Kronborg, 2001; Zutler & Holty, 2011). Methadone does not cause damage to any of the major organs or systems of the body and those side effects that do occur are considerably less harmful than the risks of tobacco, alcohol and unsanctioned opiate use.

LINK

2.3.7 Adverse effects

Product and consumer information available from https://www.ebs.tga.gov.au

2 Treatment approaches in Australia

The major hazard associated with methadone is the risk of overdose This risk is particularly high at the time of induction to MMT, and when methadone is used in combination with other sedative drugs. The relatively slow onset of action and long half-life mean that methadone overdose can be deceptive and toxic effects may become life threatening many hours after ingestion (R. Humeniuk, et al., 2000). Because methadone levels rise progressively with successive doses during induction into treatment, most deaths in this period have occurred on the third or fourth day of treatment.

LINK
Overdose in 2.3.7

Availability

Methadone is listed under Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons and is registered on the Australian Register of Therapeutic Goods as Methadone Syrup (5mg/ml) for the treatment of dependence on opioid drugs, and as Biodone Forte solution (5mg/ml) for the detoxification and maintenance treatment of dependence on opioid drugs. Methadone tablets and injections are registered in Australia for analgesia but not for the treatment of opioid dependency.

Two preparations are available for opioid substitution treatment in Australia:

- Methadone Syrup® which contains 5mg/ml methadone hydrochloride, sorbitol, glycerol, ethanol (4.75%), caramel, flavouring and sodium benzoate.
- Biodone Forte® which contains 5mg/ml methadone hydrochloride and permicol-red colouring.

Methadone can be dispensed in syrup or solution form and should be taken orally under supervision. Methadone tablets (Physeptone®) are registered in Australia for analgesia but not for the treatment of opioid dependence. It should also be noted that Physeptone® tablets are not funded under Section 100 of the Pharmaceutical Benefits Scheme (PBS), and are a restricted benefit. Permits may be required under jurisdicational regulations for the prescription of Physeptone® tablets.

2.1.2 Buprenorphine

Buprenorphine is a derivative of the morphine alkaloid, thebaine. Buprenorphine has been used in many countries (including Australia) since the 1980s as a pain-relieving drug. The use of buprenorphine for treating opioid dependence started in the 1980s and the sublingual tablet formulation of buprenorphine has since been approved for the treatment of opioid dependency in more than 40 countries (Carrieri et al., 2006). The film preparation of buprenorphine-naloxone was released in Australia in 2012.

Buprenorphine is often called a mixed agonist/antagonist drug but is more accurately described as a partial opioid agonist with high receptor affinity. It has actions similar to the full agonist drugs but with less efficacy (Walsh, Preston, Bigelow, & Stitzer, 1995; Walsh, Preston, Stitzer, Cone, & Bigelow, 1994) such that increases in dose have progressively less increase in effect. Dose increases beyond that required to saturate all receptor sites (usually 16mg) will cause a prolonged duration of action with the consumption of other opioids having little or no further effect.

2 Treatment approaches in Australia

Buprenorphine has a higher affinity for mu-opioid receptors than full opioid agonists. Because of this, buprenorphine can block the effects of other opioid agonists in a dose-dependent fashion. By its dual effects of reducing craving and attenuating the response to opioid drugs, buprenorphine reduces the self-administration of opioids. Methadone, a full opioid agonist, also reduces the impact of additional opioid drugs, but the effect of methadone is primarily due to the development of cross-tolerance which is dose dependent. In contrast buprenorphine achieves its effect primarily by prolonged occupancy of a high proportion of opioid receptors, attenuating the effects of additional opioid drugs.

Buprenorphine also exhibits antagonist effects at the kappa (κ) opioid receptor. The role of these receptors in humans remains poorly understood.

Absorption and duration of action

Buprenorphine is a long-acting drug with a terminal elimination half-life of 24 to 32 hours (Chiang & Hawks, 2003). Peak clinical effects occur one to four hours after sublingual administration. Typically effects will continue to be experienced for up to 12 hours at low doses (2 mg), but as long as 48 to 72 hours at higher doses (16 or 32 mg). The prolonged duration of effect at high doses enables alternate-day and even 3-days-a-week dispensing regimens.

Onset and duration of response to buprenorphine	
Onset of effects	30-60 minutes
Peak clinical effects	1-4 hours
Duration of effects (low dose)	8-12 hours at low dose (e.g. 2mg)
Duration of effects (high dose)	24-72 hours at high dose (e.g. >16mg)

Studies of the bioavailability of sublingual buprenorphine have found considerable between-subject variability, and differences for chronic compared to acute dosing (Chiang & Hawks, 2003; Strain, Moody, Stoller, Walsh, & Bigelow, 2004). The bioavailability of sublingual buprenorphine is largely dependent on the time the drug is in contact with the oral mucosa and appears to improve as individuals practice taking their medication.

Females exposed to the same doses of buprenorphine as males have higher blood concentrations of buprenorphine and active metabolites. The difference is likely to be due to differences in body composition, and is considered unlikely to be a critical concern for normal therapy (Moody, Fang, Morrison, & McCance-Katz, 2011).

Metabolism

Peak plasma concentrations are achieved one to two hours after sublingual administration. Buprenorphine undergoes extensive first pass metabolism when taken orally. The major metabolite, norbuprenorphine, has some opioid activity but the extent of its contribution to the effects of buprenorphine is unknown.

2 Treatment approaches in Australia

Buprenorphine is principally metabolised by two hepatic pathways: conjugation with glucuronic acid and N-dealkylation, mediated by the cytochrome P450 3A4 isozyme. The metabolites are excreted in the biliary system, with enterohepatic cycling of buprenorphine and its metabolites. Most of the drug is excreted in the faeces and, to a lesser extent, in the urine.

Safety and side effects

Unlike methadone, the effect of buprenorphine on respiratory depression reaches a ceiling, with higher doses not increasing respiratory depression to a significant degree. This action appears to make buprenorphine safer than methadone in overdose. However, even low doses of buprenorphine can be toxic when combined with sedatives such as benzodiazepines and alcohol (Faroqui, Cole, & Curran, 1983; Forrest, 1983; Papworth, 1983; Sekar & Mimpriss, 1987)

LINK
Overdose in 2.3.7

Dose response studies show that high doses of buprenorphine (16mg daily or more) do not result in substantially greater peak opioid effects than lower doses (8 or 12mg) (Walsh, et al., 1995). Doses many times greater than normal therapeutic doses appear to be well-tolerated in most individuals, and rarely result in clinically-significant respiratory depression, except in individuals who are not opioid tolerant.

Precaution should be exercised when buprenorphine is administered concomitantly with CYP3A4 inhibitors (e.g. protease inhibitors, some drugs in the class of azole antimycotics such as ketoconazole, calcium channel antagonists such as nifedipine, and some antiviral medications such as Atazanavir) as this may lead to increased plasma concentrations of buprenorphine.

LINK
A4.4.5 Drug interactions
Drug interactions in 2.3.7
Appendix 3

The side effects of buprenorphine are similar to those of other opioids (Lofwall, Stitzer, Bigelow, & Strain, 2005), the most common being constipation, disturbed sleep, drowsiness, sweating, headaches, nausea and reduced libido.

Many patients report less sedation on buprenorphine than on methadone. Users describe buprenorphine, as compared to methadone, as facilitating “more normal” levels of daily activity, leaving them more clear-headed and able to make decisions (Fischer et al., 1999; Holt, et al., 2007). However, this may not be acceptable to all patients, some of whom may benefit from the sedative and anxiolytic effect of methadone (e.g. those experiencing the symptoms of post-traumatic stress disorders).

Research evidence suggests that buprenorphine has minimal effect on psychomotor performance (Lenne, Dietze, Rumbold, Redman, & Triggs, 2003; Mintzer, Correia, & Strain, 2004), and less effect than methadone (Soyka et al., 2005) or slow release oral morphine (Giacomuzzi, Haaser, Pilsz, & Riemer, 2005). Any effect is likely to be greatest during the early stages of treatment or following dose increases. At such times patients should be advised to exercise caution in driving or operating machinery.

LINK
Driving in 2.6.11

2 Treatment approaches in Australia

There have been some reports of acute hepatitis following buprenorphine use (Herve et al., 2004; Saxon et al., 2013). However, a recent randomised controlled trial comparing buprenorphine/naloxone with methadone for treatment of opioid dependence found no evidence of liver damage during the initial six months of treatment with either medication (Saxon, et al., 2013). Baseline infection with hepatitis C or B was the only significant predictor of moving from low to elevated transaminase levels.

Precipitated withdrawal

Under certain circumstances, buprenorphine may precipitate opioid withdrawal symptoms one to four hours after the first dose (Rosado, Walsh, Bigelow, & Strain, 2007). It has a higher affinity and lower intrinsic activity than full agonists such as methadone, morphine or heroin. Consequently, buprenorphine displaces agonists from opioid receptors and, in the short term, may not produce sufficient agonist effects to compensate for the displaced opioid, producing withdrawal as the buprenorphine reaches its peak effects, approximately one to four hours after initial administration (Clark, Lintzeris, & Muhleisen, 2002; Gourarier et al., 1996; Jacobs & Bickel, 1999; Johnson, Strain, & Amass, 2003). The phenomenon of precipitated withdrawal has particular relevance during induction of buprenorphine treatment. It can largely be avoided by using appropriate dose induction procedures (Rosado, et al., 2007).

LINK

2.3.5 Induction into substitution treatment

Availability

Buprenorphine (as Subutex®) was included on the Australian Register for Therapeutic Goods in October 2000. A second sublingual tablet preparation, Suboxone®, containing buprenorphine and naloxone (the combination preparation) was approved by the Therapeutic Goods Administration on 27 July 2005. Buprenorphine is listed under Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons for the management of opioid dependence within a framework of medical, social and psychological treatment. Buprenorphine is indicated for use in maintenance and detoxification of opioid dependence.

Two sublingual tablet formulations are currently available: the mono preparation (Subutex®) contains buprenorphine hydrochloride in 0.4, 2 and 8mg strengths; the combination preparation (Suboxone®) contains buprenorphine hydrochloride and naloxone hydrochloride in a ratio of 4:1. Suboxone is available in two dose strengths: 2mg buprenorphine and 0.5mg naloxone, and 8mg buprenorphine and 2mg naloxone. A film preparation of buprenorphine-naloxone became available in Australia in 2012 and will become the only formulation of buprenorphine-naloxone available in Australia (the tablet formulation is scheduled to be removed from the market in 2013). It is easier to supervise administration of the film preparation, compared to tablets (Lintzeris et al., 2013), making this preparation less likely to be diverted.

The general chemical name ‘buprenorphine’ is used for information that applies to either preparation. Where it is necessary to distinguish between the preparations, the terms “buprenorphine” or “mono preparation” are used for Subutex® and “buprenorphine-naloxone” or “combination preparation” are used for Suboxone®.

2 Treatment approaches in Australia

The properties of buprenorphine and naloxone are such that, when taken sublingually, buprenorphine-naloxone will act as if it was buprenorphine alone. However, if the combined preparation is injected, the naloxone will have a clinically significant effect such that it is likely to attenuate the effects of the buprenorphine in the short-term, and is also likely to precipitate withdrawal symptoms in opioid-dependent individuals using other opioid drugs. These properties of the combination preparation are intended to limit the potential misuse and diversion of buprenorphine as buprenorphine-naloxone combination preparations are less likely to be injected than mono preparations containing only buprenorphine (Degenhardt, Larance, et al., 2009; Larance et al., 2011).

Research evidence indicates that the mono and combination buprenorphine preparations are largely interchangeable (Chiang & Hawks, 2003; A. Elkader & Sproule, 2005; Mendelson & Jones, 2003).

The combination preparation should not be used in women who are pregnant or breastfeeding or for patients with a proven allergy to naloxone.

LINK

A7.1 Pregnancy and breastfeeding

2.6.3 Pregnancy and breastfeeding

Buprenorphine is also registered in Australia as Temgesic® sublingual tablets and ampoules for intramuscular and subcutaneous injection, for short-term (not more than one week) relief of moderate to severe pain, including post-operative and terminal and chronic pain. Buprenorphine is also available in Australia as transdermal patches for pain relief. These are not approved for use in the treatment of opioid dependence and deliver doses that are too low (5, 10 and 20ug/h) for effective substitution treatment.

2.1.3 Naltrexone

Naltrexone was first used in the treatment of opioid dependence in the USA in the 1970s. However, because there was seen to be only a small demand for the drug, it was not initially registered for use in Australia. During the 1990s there was an increase in the prevalence of opioid dependence, and increasing interest in using naltrexone. A number of medical practitioners began using the Special Access Scheme (which under certain circumstances allows the prescribing of unregistered drugs) to use naltrexone. Results of the first Australian clinical trial of naltrexone in the management of opioid dependence were published in 1998. In 1999, the drug was registered for use in Australia.

Naltrexone is an opioid antagonist. Opioid antagonists bind to opioid receptors, without producing opioid effects, and block both the analgesic and euphoric effects of opioid agonists, such as heroin, on the receptor sites. Naltrexone is a highly specific opioid antagonist which has a high affinity for opiate receptor sites. It competitively displaces opioid agonists if they are present, such as methadone, heroin, and slow-release morphine. However, naltrexone has less effect on the so-called “supra agonists”, which are those opioid drugs with very high affinity for opioid receptors. These include buprenorphine and fentanyl derivatives.

Naltrexone has few intrinsic actions besides its opioid-blocking properties. It does produce some papillary constriction by an unknown mechanism. Naltrexone does not cause any physiological tolerance or dependence. It is not known to block the effects of other classes of drug besides opioids, although it has some effect on the subjective effects of alcohol. The positive reinforcing effects of alcohol are thought to be mediated through opioid pathways and this is the basis of action of naltrexone in relapse prevention treatment of alcohol dependence (Heinz, Beck, Grusser, Grace, & Wrase, 2008).

2 Treatment approaches in Australia

Naltrexone is rapidly absorbed, with peak blood levels achieved about one hour after oral administration (Gonzalez & Brogden, 1988). Naltrexone has a relatively short plasma half-life of four hours. It is primarily metabolised in the liver to 6-β-naltrexol, which has a plasma half-life of about 10 hours and is also an opioid antagonist. Approximately 20% of the active metabolite is bound to plasma protein, and is distributed widely, with relatively high amounts in the brain, fat, spleen, heart, testes, kidney and urine (Gonzalez & Brogden, 1988). Naltrexone and 6-β-naltrexol undergo enterohepatic recycling and are excreted primarily by the kidney. Less than 1% of naltrexone is excreted unchanged.

Despite both compounds having relatively short half-lives, the duration of naltrexone blockade is much longer. An oral dose of 50mg naltrexone has been shown to produce blockade of opioid receptors with a half-time of 72 to 108 hours (Lee et al., 1988).

Availability

Naltrexone is listed in Schedule 4 of the *Standard for the Uniform Scheduling of Medicines and Poisons*. Naltrexone was entered in the Australian Register of Therapeutic Goods in January 1999, as ReVia® film-coated tablets (50mg). ReVia® is registered in Australia for use as part of a comprehensive treatment program for alcohol dependence and as an adjunctive therapy in the maintenance of formerly opioid dependent patients who have ceased the use of opioids (detoxified).

Naltrexone is available on the Pharmaceutical Benefits Schedule (PBS) for only one indication, as an authority prescription for relapse prevention in the management of alcohol dependence, but the PBS notes that naltrexone is contraindicated in patients receiving opioid drugs. Multiple studies have demonstrated the efficacy of naltrexone in alcohol dependence, although the effectiveness is modest at best (Rosner et al., 2010).

Naltrexone is available on private prescription for relapse prevention in opioid dependence. This is treatment designed to assist a detoxified and opioid-free former user to remain abstinent from opioid drugs.

LINK

A3 Detoxification

2.2.3 Medications to manage withdrawal

Naltrexone has been used to accelerate the process of withdrawal from opioids but this is an “off-label” use of the drug – the approved Australian Product Information for naltrexone contraindicates its use in “patients in acute opioid withdrawal”.

Because the major limitation of naltrexone is patient compliance with the daily regimen, there is considerable interest in the use of depot and implant preparations of naltrexone, designed to slowly release naltrexone into the circulation over a period of weeks to months. Medical practitioners in Australia and elsewhere have experimented with naltrexone implants designed to do this.

Depot and implant preparations of naltrexone are not currently registered in Australia. A sustained-release (depot) preparation was approved in the USA for treatment of opioid dependence in October 2010, but similar approvals have not yet been sought in Australia.

2 Treatment approaches in Australia

The National Health and Medical Research Council in 2011[16] concluded that evidence for the effectiveness of naltrexone implants for the treatment of opioid dependence is at an early stage and as such, naltrexone implants should only be used in a research setting. Position statements on naltrexone sustained-release preparations (injectable and implants) released by the Australian National Council on Drugs in March 2012 and by the Royal Australasian College of Physicians in April 2013 included the following points:

- only pharmacological treatments that are registered as safe and efficacious should be available for routine use;
- for pharmacological treatments that do not have TGA approval, formal registration processes through the approved clinical trial procedures should be followed;
- ongoing use of the TGA Special Access Scheme for sustained release naltrexone preparations circumvents formal processes to ascertain quality, safety and efficacy of pharmacological treatment products and is therefore inappropriate;
- given the very limited Australian data and evidence on the efficacy and safety of sustained release naltrexone preparations, their authorised use through the TGA Special Access Scheme is ethically problematic as it puts patients at risk of unknown harms for an unknown benefit.

Given the unproven, experimental nature of sustained-release preparations of naltrexone, it is particularly important that full and informed consent is obtained prior to such treatment being provided. The information given prior to treatment should make it clear that the treatment is experimental and unproven.

2.2 Detoxification

2.2.1 Nature of opioid withdrawal

Withdrawal occurs when the drug of dependence is eliminated from the body, and any physical adaptation that has occurred as a consequence of dependent drug use is reversed. Signs and symptoms of withdrawal usually begin two to three half-lives after the last opioid dose, i.e. 36-48 hours for long half-life opioids such as methadone, and 6-12 hours for short half-life opioids such as heroin and morphine. The nature and duration of withdrawal experienced is influenced by the drug of dependence, and the severity of dependence. Drug withdrawal causes clinically significant distress and impairment in social, occupational, or other important areas of functioning.

[16] www.nhmrc.gov.au/your-health/naltrexone-implants, accessed 8 February 2013

2 Treatment approaches in Australia

Opioid dependence is typically associated with a well-defined pattern of withdrawal symptoms, as indicated in the table below:

Time since last heroin use	Common symptoms
6 to 12 hours	• runny eyes and nose, sneezing, yawning • sweating
12 to 24 hours	• agitation and irritability • goosebumps • sweating, hot and cold flushes • loss of appetite
More than 24 hours	• strong urges (cravings) to use heroin • stomach cramps, diarrhoea • poor appetite, nausea, vomiting • back pain, pain in joints, legs or arms, headache • poor sleep • lethargy, fatigue • restlessness, irritability, agitation • poor concentration • hot and cold flushes, increased sweating
2nd to 4th days	Symptoms reach their peak
5th to 7th days Second week	Most physical symptoms begin to settle down; appetite returns 'Physical' discomfort subsiding; may have ongoing problems with poor sleep, tiredness, irritability, cravings, low mood
Weeks to months	Improvements in sleep, levels of activity and mood; and general health, and reduced cravings

The duration of methadone withdrawal is longer (5 to 21 days) than withdrawal from heroin or other short-acting opioids.

The first or acute phase of withdrawal may then be followed by a protracted withdrawal syndrome which is characterised by a general feeling of reduced wellbeing. During this period strong cravings for opioids may be experienced periodically.

Opioid withdrawal is unpleasant, though not usually life-threatening in physically fit people, provided adequate hydration and electrolyte levels are maintained. It can, however, significantly complicate medical or psychiatric conditions. Completion of withdrawal is difficult for most people. Untreated methadone withdrawal symptoms may be perceived as more unpleasant than heroin withdrawal, reflecting the more prolonged nature of methadone withdrawal. Factors that have been identified as having the potential to influence the severity of withdrawal include the duration of opioid use, general physical health and psychological factors, such as the reasons for undertaking withdrawal and fear of withdrawal.

LINK

Appendix 2: Assessment of opioid withdrawal

Appendix 5: Withdrawal states from commonly used drugs

2 Treatment approaches in Australia

The partial agonist properties of buprenorphine, along with its slow dissociation from opioid receptors result in a withdrawal syndrome that is delayed and may be milder than withdrawal from heroin, morphine and methadone (Horgan, 1989; Jasinski, 1981; Jasinski et al., 1982; Mello & Mendelson, 1980; Mudric, Strain, Stitzer, & Bigelow, 1998; San et al., 1992).

2.2.2 Aim of detoxification

Many drug users, their parents and the general community believe that ending dependence is simply a matter of ceasing use and detoxifying the body. As such, they see detoxification as a treatment. However, experience in many different countries has shown that, no matter what the drug, relapse following detoxification is extremely common unless followed by an abstinence-oriented treatment. Furthermore, many dependent drug users find it difficult to complete detoxification.

Detoxification addresses the physical adaptation of dependence but does not address the psychosocial aspects. Detoxification alone is not a treatment but it is an important point of contact between dependent opioid users and treatment services. It represents a necessary stepping stone from dependence to drug-free treatment.

Drug users will differ in their reasons for seeking detoxification, and will be at different stages of change. Users may seek detoxification as a break from drug use, or in an attempt to regain control over their drug use, without any serious intention of longer term change. Others, particularly those who have participated in a period of substitution or psychosocial treatment prior to detoxification, may be well progressed in behavioural change (L. Gowing, et al., 2001).

Given the diversity of reasons for seeking detoxification, and the chronic relapsing nature of drug dependence, it is not surprising that rates of relapse following detoxification tend to be high. However, detoxification also provides a limited opportunity for interventions which may encourage users to move towards the next stage of change, and at least a period of respite from the risks associated with regular drug use as well as promoting engagement in further treatment.

Some people believe that experiencing the discomfort of withdrawal will help to deter users from returning to regular opioid use. There is no evidence to support this belief. Indeed, most chronic opioid users will experience withdrawal symptoms many times, and rather than being a deterrent, the knowledge that opioid use will alleviate withdrawal symptoms becomes a source of reinforcement for continued use.

2.2.3 Medications to manage withdrawal

There are four major types of intervention to manage opioid withdrawal:

- abrupt cessation and symptom amelioration using non-opioid drugs (usually alpha-2 adrenergic agonists such as clonidine);
- symptom amelioration using buprenorphine;
- reducing doses of methadone; and
- induction of withdrawal using opioid antagonists (naltrexone or naloxone), also known as antagonist-induced withdrawal or rapid detoxification (L. R. Gowing & Ali, 2006).

2 Treatment approaches in Australia

Approaches based on clonidine or reducing doses of methadone were accepted internationally as standard opioid detoxification modalities for many years, although methadone has not been widely used in Australia for detoxification. Approaches using buprenorphine have emerged in the last 10 years as buprenorphine has become more widely available. With evidence of the greater effectiveness of buprenorphine compared to clonidine (L. Gowing, R. Ali, & J. White, 2009a) this has become the preferred medication for managing opioid withdrawal in Australia.

Supplementary medications, such as benzodiazepines for sleep disturbance and anxiety, anti-emetics, anti-diarrhoeals, muscle relaxants and non-opioid analgesics, are often used in combination with these major medication approaches in response to symptoms experienced.

Adrenergic agonists

Alpha2-adrenergic agonists, such as clonidine, help control agitation and restlessness. However, the dose which can be employed is limited by side effects. Most patients will become somewhat hypotensive and patients should be warned of this risk.

When opioid withdrawal is managed with clonidine, rates of completion of withdrawal are similar to, or lower than, completion rates when withdrawal is managed with reducing doses of methadone over 21 days or less|★★★| (L. Gowing, et al., 2009a). The severity of withdrawal is also similar for the two types of treatment, but the pattern of withdrawal is different – symptoms emerge early during treatment with clonidine, while significant symptoms do not emerge until methadone doses drop below 10mg/day (Cushman, 1974; Gossop, Griffiths, Bradley, & Strang, 1989). More participants drop out early in treatment with clonidine, reflecting the early emergence of withdrawal symptoms, the concomitant occurrence of peak side effects, and participants' preference for opioid drugs (L. Gowing, et al., 2009a).

In the management of opioid withdrawal, clonidine is typically administered orally as two to four doses per day, with the total dose adjusted daily according to withdrawal symptoms and side effects (particularly blood pressure). A test dose of 150ug is often administered to check for hypotensive effects. If tolerated, treatment is continued at 12-15ug/kg/day in four divided doses. Maximal doses are generally required for only a few days around the time of maximum withdrawal, usually two to four days after cessation of opioids. Doses are then tapered and ceased seven to ten days after cessation of opioids (L. Gowing, et al., 2009a).

Buprenorphine

Buprenorphine can be used in withdrawal from heroin, methadone and other opioids.

The intensity of opioid withdrawal is significantly less when managed with buprenorphine, compared to clonidine |★★★★|. Buprenorphine is associated with greater retention in treatment, as indicated by a longer mean duration of treatment. Patients treated with buprenorphine remain in treatment for 1 or 2 days longer, relative to clonidine, for each week of scheduled treatment. Completion of withdrawal is significantly more likely when withdrawal is managed with buprenorphine rather than

2 Treatment approaches in Australia

clonidine, in either an inpatient or outpatient setting |★★★★|. Compared to clonidine, buprenorphine is associated with fewer adverse effects and fewer premature withdrawals from treatment due to adverse effects (L. Gowing, et al., 2009a).

Buprenorphine is equivalent to methadone in alleviation of withdrawal symptoms, and withdrawal may resolve more quickly with buprenorphine |★★|. There is a trend towards more successful completion of withdrawal with buprenorphine compared with methadone (L. Gowing, et al., 2009a). Buprenorphine is superior to methadone for relief of opioid withdrawal symptoms when opioid and benzodiazepine withdrawal is carried out concurrently (A. R. Lingford-Hughes, Welch, Peters, & Nutt, 2012).

Buprenorphine is particularly useful in managing opioid withdrawal, in that it is not only effective during the withdrawal period, but also facilitates links to post-withdrawal treatment. The use of buprenorphine for several days generally alleviates withdrawal symptoms without significant sedation, thereby allowing patients and clinicians to examine post-withdrawal issues relatively early on in the withdrawal episode. Patients who are not interested in ongoing pharmacotherapy treatment can cease after a short course of buprenorphine with minimal rebound discomfort. Alternatively, those patients who want to extend the duration of their withdrawal program, or have reconsidered the role of an opioid substitution treatment program, can continue buprenorphine treatment over a longer period of time. Another benefit of buprenorphine is that naltrexone can be initiated after buprenorphine administration with less delay and less severe withdrawal than is the case following methadone treatment.

LINK

2.4.2 Initiating naltrexone treatment

Tapered methadone

Tapered methadone is effective in reducing withdrawal |★★★|, but symptoms differ according to the medication used and the detoxification program followed (Laura Amato et al., 2013). Opioid withdrawal managed with reducing doses of methadone is associated with reasonable rates of completion of withdrawal, reduction of symptoms to tolerable levels, and minimal adverse effects. Opioid withdrawal, managed with reducing doses of methadone, is more likely to be completed if withdrawal is scheduled to occur over a short period of time (21 days or less). Control by the clinician, rather than the patient, of the rate of reduction of methadone dose is associated with greater reductions in methadone dose. Patient control of dose levels in the context of methadone maintenance treatment is seen as beneficial through enhancement of patient trust and responsibility. This may have less relevance to an episode of short-term methadone prescription to manage withdrawal. However, other factors may also be relevant to the lower success rate of patient-regulated withdrawal, including anxiety about withdrawal symptoms and a reluctance to cease opioid use.

Methadone for the management of opioid withdrawal is generally commenced at doses of 10-20mg daily, according to the severity of dependence and degree of tolerance to opioids. The dose is then reduced by 1-2mg/day, with methadone ceased in around 10 days. Withdrawal symptoms are reduced by this type of regimen, but not eliminated, and some symptoms will continue to be experienced in the week following cessation of methadone (WHO, 2009).

2 Treatment approaches in Australia

Tapered doses of slow-release oral morphine may be used in the same way and may have similar effectiveness to tapered methadone for the management of opioid withdrawal (Madlung-Kratzer, Spitzer, Brosch, Dunkel, & Haring, 2009).

Use of opioid antagonists in detoxification

Antagonist-induced withdrawal was promoted as an answer to opioid dependence in the 1990s (Bearn, Gossop, & Strang, 1999; Gossop & Strang, 1997; Simon, 1997). The published literature on rapid detoxification is characterised by a marked variation in approaches used, in reported outcomes, in reported severity of symptoms associated with detoxification and in medium term outcomes. Broadly speaking, two approaches to rapid detoxification have evolved:

- Rapid detoxification under anaesthesia; and
- Rapid detoxification using minimal sedation (patient rousable).

The administration of opioid antagonists (such as naloxone or naltrexone) to an individual who is currently physiologically dependent on opioids precipitates an immediate abstinence syndrome, often of considerable severity.

The acute phase of precipitated withdrawal involves two major clusters of symptoms:

- Gastrointestinal symptoms – vomiting and diarrhoea, often with cramping abdominal pain, lasting many hours
  - Without supportive treatment patients may become dehydrated and develop electrolyte disturbances as a result of severe vomiting;
- Psychological disturbances, with agitation, dysphoria, and delirium
  - Delirium can last for up to 12 hours;
  - Significant physiological disturbances, including a marked increase in circulating catecholamines.

The trade off is that some aspects of antagonist precipitated withdrawal appear to be of shorter duration than the process of spontaneous withdrawal. However, while acute signs of withdrawal subside within 4 to 6 hours, many patients remain ill for considerably longer than this.

A systematic (Cochrane) review (L. Gowing, Ali, & White, 2010) found that antagonist-induced withdrawal under heavy sedation, compared to light sedation, does not confer additional benefits in terms of less severe withdrawal symptoms or increased rates of commencement on naltrexone maintenance treatment. Given that the adverse events are potentially life-threatening, the value of antagonist-induced withdrawal under heavy sedation or anaesthesia is not supported |★★★★|. The high cost of anaesthesia-based approaches, both in monetary terms and use of scarce intensive care resources, suggest that this form of treatment should not be pursued.

A second systematic (Cochrane) review (L. Gowing, R. Ali, & J. M. White, 2009b) concluded that the use of opioid antagonists combined with alpha2-adrenergic agonists (such as clonidine) under minimal sedation is a feasible approach to the management of opioid withdrawal and may be suitable for those with a clear commitment to abstinence and good support, who intend to enter antagonist-maintenance treatment. This approach is probably associated with higher rates of commencement of naltrexone maintenance treatment, but there are insufficient data to determine the extent and duration of benefit relative to other forms of withdrawal treatment |★★|. A high level of monitoring and support is desirable for several hours following administration of opioid antagonists because of the possibility of vomiting, diarrhoea and delirium (L. Gowing, et al., 2009b).

2 Treatment approaches in Australia

2.2.4 Setting for detoxification

Withdrawal from alcohol and other drugs can be managed in a variety of clinical and community settings depending on the individual's needs and circumstances, health risks and severity of withdrawal. Not all settings are suitable or necessary for all people. It is a case of balancing individual needs and preferences with cost effectiveness and access. Such settings include home-based, outpatient and inpatient withdrawal management. Inpatient withdrawal is more expensive, but is associated with higher rates of treatment completion.

Outpatient withdrawal generally involves daily attendance at a clinic for assessment and medication. Outpatient withdrawal is appropriate where there is a supportive home environment and where withdrawal is unlikely to be medically complicated. Home-based withdrawal generally involves the patient being visited at home by a nurse or other support worker. The staff time and travel costs associated with home-based withdrawal make this approach less cost effective.

Treatment setting is a significant factor influencing the outcome of a detoxification episode, but there have been very few direct comparisons of different settings for opioid withdrawal. A Cochrane review (Day, Ison, & Strang, 2008) found only one study (from 1975) that met the criteria for inclusion. Looking across studies, rates of completion are consistently higher when detoxification is undertaken on an inpatient, compared to outpatient, basis. However, it is unclear how long the differential in rates of abstinence might be maintained. Generally high rates of relapse in the first weeks following discharge indicate the need for follow-up treatment to make best use of the advantage offered by inpatient detoxification (L. Gowing, et al., 2001). Clinical experience tells us that for outpatient withdrawal to be successfully completed, the patient needs to be strongly motivated, the environment needs to be suitable and appropriate support available. An inpatient setting is most appropriate for those significantly impacted by dependence and with limited family support.

Factors such as stable home situation, support from family and frequency of contact with the clinical team can influence the outcome of a detoxification episode. For example, in one study in Israel (Lerner, Gelkopf, Oyffe, & Sigal, 1995) clonidine was used for home-based detoxification in Israel and assisted 96% of participants in completing withdrawal. Drop-out in the 12 months following detoxification was also low at 8%. Participants in the study were in a stable home situation, received substantial support from family and had daily contact with the clinical team. In contrast, in another study, 39% completed home-based withdrawal managed with lofexidine, an analogue of clonidine (A. S. Brown & Fleming, 1998). Only 19 of the 28 participants in this study had a resident supporter, with 11 of those supporters also being drug users. In addition, contact with the clinical team was less frequent (three to four times a week).

Completion rates tend to be higher for withdrawal from methadone compared to withdrawal from heroin. At the same time, there is evidence that withdrawal from methadone is more prolonged and more severe. It is likely that stabilisation of health and social status associated with methadone maintenance treatment provides better preparation for withdrawal and consequently increases the probability of completion of withdrawal (L. Gowing, et al., 2001).

2 Treatment approaches in Australia

Commencing an outpatient withdrawal requires planning, and the mobilisation of the necessary supports and services. Patients should prepare themselves and their environment in advance, to maximise their chance of 'success'. For example, it is very hard to get through withdrawal in the company of others still using heroin. A safe environment should be organised at the beginning of the withdrawal episode. A 'safe' place is one where there won't be any drugs easily accessible, and where patients will not be confronted by other drug users. It is important to have caring people to support a patient during withdrawal, and these support people themselves need guidance and information about the process, and suggestions as to what they can reasonably do to help.

2.2.5 Adjunct therapies in detoxification

Many patients will want to deal with a range of personal, emotional or relationship problems during the withdrawal episode, but they should be persuaded to defer all this until later. Attempting to work through such issues will almost certainly be emotionally painful and anxiety-provoking, which just intensifies cravings and withdrawal and puts the whole withdrawal program in jeopardy. Furthermore, patients in withdrawal tend to be irritable, agitated, tired and run-down; they can suffer from mood swings and poor sleep patterns, as well as having difficulty in concentrating. This is definitely not the optimal frame of mind in which to try to solve significant, long-standing life problems. Patients should be assured that, while they have many important issues to work through to get their lives together again, they should take one step at a time. There will be opportunities for these wider problems to be addressed as part of their ongoing rehabilitation after they get through withdrawal. However, crisis intervention may be required during a withdrawal episode to ensure adequate accommodation, food or other urgent welfare issues.

LINK
2.5 Adjunct therapies

A Cochrane review (L. Amato, Minozzi, Davoli, & Vecchi, 2011a) found that adding any psychosocial treatment to any detoxification treatment was beneficial in terms of reduced dropouts, use of opiates during treatment and at follow-up, and clinical absences during treatment. However, in the studies included in the review, psychosocial interventions were delivered in conjunction with methadone or buprenorphine over periods ranging from 16 days to 26 weeks. With short-term detoxification (10 days or less), support is important, but the capacity for psychosocial interventions is doubtful.

2 Treatment approaches in Australia

2.2.6 Selection of approach

Treatment selection is a synthesis of:

- assessment of the patient
- examination of the available treatment options and likely outcomes and
- negotiation with the patient around a suitable treatment pathway.

In considering possible modalities, it is important to remember that many people come for treatment with misconceptions and/or inadequate information about the options available. In general, withdrawal treatment is appropriate for those who are considering abstinence-oriented, post-withdrawal treatment (such as naltrexone, residential rehabilitation, counselling or 12-step programs), or for those who are not interested in longer-term treatment, and merely want a 'break' from dependent opioid use.

The presence of polydrug dependence is an important consideration in selection of withdrawal approach as the patient will experience two different withdrawal syndromes simultaneously. Consideration needs to be given to the risks associated with concurrent withdrawal from multiple drugs and a decision may be made that this should be done sequentially rather than concurrently. Specialist medical advice should be sought in such situations.

The pressures and strains of using drugs, key life events ('turning points') and the availability of social support are important factors impacting on the likelihood of successful withdrawal. The exact detoxification technique used is less important (Day, 2012).

However, opioid substitution treatment (with methadone or buprenorphine) may be more appropriate for those with significant heroin dependence who will not accept residential rehabilitation or naltrexone treatment, but nevertheless want to stop or permanently reduce their heroin use and the damage it is causing them.

Clinical decision-making should be supported by evidence, and patients should be presented with the relative evidence, i.e. the merits and limitations of treatment outcomes associated with each approach. Within such a framework, there is widespread evidence suggesting that opioid substitution treatment is the 'gold standard' for most people with chronic heroin dependence, by virtue of its success in keeping patients in treatment, and reducing drug-related harms.

No matter what the form of withdrawal or the setting, relapse is common. Follow-up treatment and support is important. Transfer to substitution treatment is a good outcome for those unable to sustain abstinence immediately – an integrated treatment system should facilitate this.

2 Treatment approaches in Australia

2.3 Agonist pharmacotherapy (opioid substitution treatment)

Methadone is the most established and most evaluated medication used for opioid substitution treatment. Buprenorphine was introduced more recently but is now in widespread use as an alternative to methadone. Slow-release oral morphine is under investigation and may offer some advantages over methadone and buprenorphine but its effectiveness is not yet established. Levo alpha-acetyl methadol (LAAM) was used as a longer-acting alternative to methadone but concerns about possible adverse effects on heart rhythm led to its withdrawal from the market.

LINK
Substitution treatment in 1.2.4

Substitution treatment is generally considered for dependent users who find it difficult to stop their drug use and complete withdrawal. Where dependence does not exist, other forms of treatment should be considered.

2.3.1 Aims of substitution treatment

The value of substitution treatment lies in the opportunity it provides for dependent users to stabilise their health and social functioning and reduce their exposure to risk behaviours before addressing the physical adaptation dimension of dependence.

In line with this, the objectives of pharmacotherapy treatment are generally to:

- reduce or eliminate unsanctioned opioid and other drug use by those in treatment;
- improve the health and wellbeing of those in treatment;
- reduce the spread of blood-borne diseases associated with injecting opioid use;
- reduce the risk of death associated with opioid use; and
- reduce levels of involvement in crime associated with opioid use.

As with all forms of treatment, the specific goals of a particular episode of substitution treatment need to be tailored to the particular strengths and weaknesses of each individual. For some severely dependent and dysfunctional individuals, very modest goals of treatment may be appropriate, such as trying to reduce their injecting drug use, or merely ensuring that they have access to clean needles and syringes. For other people with skills and supports, goals such as abstinence from opioid drugs and a return to employment may be more appropriate.

2.3.2 Effectiveness of substitution treatment

There is consistent evidence from controlled trials, longitudinal studies and program evaluations that methadone substitution treatment for people who are opioid dependent is associated with reductions in opioid use, criminal activity (Oliver et al., 2010), deaths due to overdose, and the risk of HIV transmission (Bukten et al., 2012; Cousins et al., 2011; Degenhardt, Randall, et al., 2009; L. Gowing, Farrell, Bornemann, Sullivan, & Ali, 2011; MacArthur et al., 2012; Teesson, Havard, Ross, & Darke, 2006).

2 Treatment approaches in Australia

A systematic (Cochrane) review found that, compared to no opioid replacement, methadone maintenance treatment is significantly more effective

- in retaining patients in treatment |★★★|; and
- for reducing heroin use |★★★★| (Mattick, Breen, Kimber, & Davoli, 2009).

Randomised controlled trials are not well suited to measuring effects on criminality, morbidity and mortality, making these outcomes more difficult to quantify.

Methadone maintenance treatment does not completely abolish use of opioid drugs amongst all patients but it does substantially reduce use. The Australian Treatment Outcomes Study (ATOS) followed four cohorts of heroin users. Three cohorts were recruited as they entered treatment (opioid substitution treatment, detoxification or residential rehabilitation) while one group was not in treatment at the time of recruitment to the study. At one-year follow-up, 57% were abstinent from heroin, 65% in the opioid substitution treatment group, 52% in the detoxification group, 63% in the residential rehabilitation group and 25% in the non-treatment comparison (Teesson et al., 2006). At the three-year follow-up, 10% of participants who initially entered opioid substitution treatment and 15% who initially entered residential treatment achieved 36 months of sustained abstinence from heroin, compared to 4% who initially received detoxification (Darke et al., 2007). It should be noted that this comparison of outcome by treatment modality is not straightforward with study participants engaging in more than one treatment episode and often different types of treatment in the course of the study. Another estimate, based on research and experience in the USA, is that illicit opioid use reduces from multiple doses of heroin each day at entry to opioid substitution treatment, to less than 20% of persons using any heroin, within one year (Kreek, 2000).

The Treatment Outcomes Prospective Study (TOPS) in the United Kingdom found that retention in treatment at three months was highest for methadone maintenance treatment (65%), followed by therapeutic communities (44%) and outpatient drug-free treatment (40%). Both methadone maintenance and therapeutic community treatment were associated with reductions in drug use and criminality (W. Hall, Ward, & Mattick, 1998). Similarly, among 1503 heroin users attending public treatment centres in Italy, the retention rate after one year was 40% for methadone maintenance treatment, 18% for naltrexone and 15% in drug-free treatment. Study participants receiving 60mg/day methadone or more, and those receiving between 30 and 59mg/day, were 70% and 50% more likely, respectively, to remain in treatment than those receiving less than 30mg/day (D'Ippoliti, Davoli, Perucci, Pasqualini, & Bargagli, 1998). In the ATOS, at the one-year follow-up, 79% of those who initially entered maintenance treatment were in some form of treatment, compared with 49% of those who initially entered detoxification, and 49% of those who entered residential rehabilitation at baseline (Teesson, Ross, et al., 2006).

There is an increased risk of death (Cornish, Macleod, Strang, Vickerman, & Hickman, 2010; Cousins, et al., 2011; Degenhardt, Randall, et al., 2009) during induction onto methadone maintenance treatment – possibly up to seven times the risk prior to entry. However, once stabilisation is achieved (about two weeks) the risk of overdose death is then substantially reduced in comparison with the risk prior to treatment (Cornish, et al., 2010; Degenhardt, Randall, et al., 2009; R. Humeniuk, et al., 2000). Risk of death increases again immediately after dropout or discharge (Cousins, et al., 2011).

2 Treatment approaches in Australia

Retention in methadone maintenance treatment increases, and use of heroin decreases, with increasing methadone doses. Retention in treatment is also improved with takeaway dosing and less frequent treatment centre visits (but this must be balanced by the risk of diversion to the black market). The most effective methadone maintenance treatment programs use doses of 60mg/day or more (Faggiano, Vigna-Taglianti, Versino, & Lemma, 2003) and are oriented towards maintenance rather than abstinence (L. Gowing, et al., 2001).

Compared to no opioid replacement, buprenorphine maintenance treatment:

- is more effective in retaining opioid dependent people in treatment |★★★★|; but
- only medium (8-15mg) and high (>15mg) doses are effective in suppressing heroin use |★★★★| (Mattick, Kimber, Breen, & Davoli, 2008).

Compared to methadone maintenance:

- buprenorphine in flexible doses is less effective in retaining opioid-dependent people in treatment than medium- or high-dose methadone |★★★| (Burns et al., 2009; Mattick, et al., 2008), but these data were based on studies that used relatively slow rates of induction of buprenorphine; and
- buprenorphine in flexible doses is as effective as methadone in reducing heroin use, as determined by urine screening and self-report |★★★★| (Mattick, et al., 2008).

Despite the low incidence of side effects and the health improvements associated with methadone maintenance treatment, it does not suit all opioid-dependent people. It is estimated that about one in four people do not respond well to methadone maintenance treatment (Gossop, Marsden, Stewart, & Rolfe, 2000) for reasons relating to the patients themselves, and to the programs (Gerstein et al., 1994).

Several patient variables have been found in the research literature to be consistently associated with methadone maintenance treatment outcome. People who are younger, who have more pre-treatment criminal involvement, who are more dependent, and who have high levels of alcohol use tend to be retained in treatment for shorter periods. People who are employed pre-treatment, who are living with a spouse or family, who are motivated and have realistic expectations of treatment are more likely to be retained longer (Ward, Mattick, & Hall, 1998). Some studies have also found that previous attempts at methadone maintenance predict better outcomes (Rhoades, Creson, Elk, Schmitz, & Grabowski, 1998).

There is now substantial research evidence that opioid dependent people who do not respond to substitution treatment with methadone may achieve improved outcomes with the addition of prescribed heroin |★★★| (Egli, et al., 2009; Ferri, et al., 2011). However, this option is not available in Australia.

There is strong evidence that longer-term treatment is associated with a greater likelihood of long-term abstinence from opioid drugs than are shorter periods of treatment (Gossop, 2011). Stability and consequent improvements in drug use and psychosocial stability gained as a result of opioid substitution treatment tend to become significant after three months of treatment, with the majority of benefit gained after one year (benefits may be sustained beyond this point with continued treatment).

2 Treatment approaches in Australia

2.3.3 Choosing between methadone and buprenorphine

The evidence demonstrates that both methadone and buprenorphine are effective in the treatment of opioid dependence (WHO, 2009). Methadone has a stronger opioid effect, and is associated with greater retention in treatment, but many patients do well on buprenorphine, and may express a preference for buprenorphine. In selecting which drug to use, such preferences are important, as are the logistics of participating in treatment and the patient's general expectations of treatment.

LINK
2.3.2 Effectiveness of substitution treatment

Prior treatment experience may indicate the likely response to medications. There is considerable individual variation in absorption, metabolism and clearance of medications that is reflected in variation in response and experience of adverse effects. Individuals experiencing significant side effects from one opioid medication may benefit from treatment with an alternative medication.

Buprenorphine maintenance treatment may be more likely to support attempted withdrawal. At the same time it is relatively easy to transfer from buprenorphine to methadone if necessary, and the transition from buprenorphine to naltrexone may be easier than the transition from methadone to naltrexone (Sigmon et al., 2012).

Some longer-term side effects (e.g. impact on sex hormones, sleep apnoea, prolonged QTc interval) are more common with methadone. Drug interactions are more likely to be clinically relevant with methadone – this can be particularly relevant for patients taking medications for HIV or TB.

LINK
2.3.7 Adverse effects
A4.4.5 Drug interactions
Appendix 3: Clinically significant interactions between methadone, buprenorphine and other medications

Methadone has a more sedating effect, and some patients report greater mental 'clarity', more 'reality-oriented' thinking with buprenorphine compared to methadone (Fischer, et al., 1999). Studies of cognitive performance have found poorer performance for patients maintained on either methadone or buprenorphine compared to abstinent ex-users or non-using controls (Darke, McDonald, Kaye, & Torok, 2012) but deficits in cognitive function are more apparent with methadone early in treatment (Rapeli et al., 2007; Rapeli, Fabritius, Kalska, & Alho, 2011). Again the significance of any such differences will depend on the individual patient.

2.3.4 Psychosocial support

There is evidence that treatment factors other than an adequate dose of medication contribute to improved outcomes. In particular, the quality of the therapeutic relationship between treatment providers and patient is important. Where patients are treated respectfully, with regard to their dignity, autonomy and privacy, the outcomes of treatment are likely to be improved (Gjersing, Waal, Caplehorn, Gossop, & Clausen, 2010). In addition, some formal processes are of value.

People with a background of opioid dependence may have a range of social problems (e.g. financial, employment, parenting, legal, accommodation) and psychological difficulties (e.g. depression, anxiety). A history of physical, sexual and emotional abuse is prevalent among opioid dependent people, particularly women (Kreek, Borg, Ducat, & Ray, 2010; Mills, Lynskey, Teesson, Ross, & Darke, 2005). Addressing the consequences of abuse is an important component of recovery. The stability afforded by long-term substitution treatment provides an opportunity for these issues to be addressed.

2 Treatment approaches in Australia

Provision of opioid substitution treatment as a comprehensive program requires access to a mix of medical and counselling skills, which may be sourced through cooperative arrangements. Access to and networking with medical, psychiatric, social and harm-reduction services is desirable and should be developed when possible; however, psychosocial interventions, including counselling, may not be necessary onsite (WHO, 2009).

The evidence from methadone treatment studies suggests that counselling should be available to all patients, and that patients should be actively encouraged to avail themselves of counselling services. However, compulsory counselling is not associated with better outcomes (if anything, retention is worse). Patients think of mandatory counselling sessions as a game they have to play to keep up their supply of medication.

Methadone maintenance treatment, with or without counselling, brings about behavioural change (Schwartz, et al., 2012; Yancovitz, et al., 1991) but, compared to methadone alone, methadone plus psychosocial support is associated with greater reduction in opioid use, with no significant effect on retention (L. Amato, Minozzi, Davoli, & Vecchi, 2011b). Similarly the provision of more intensive counselling in association with buprenorphine treatment was not associated with significant improvements in treatment outcome (Mitchell et al., 2013). Findings of a recent study suggest that structured support, delivered by phone, may improve medication compliance and hence treatment outcomes (Ruetsch, Tkacz, McPherson, & Cacciola, 2012).

It is likely that not all OST patients will benefit from psychosocial support and that those most likely to benefit are those who need assistance to get some order back into their lives. This provides support for approaches that treat each person on an individual basis (Bell, 1998). However, counselling skills are also of value when not in focused, formal counselling, but in the day-to-day treatment of patients on methadone.

These skills can be useful in the prevention and management of crises. Drug users in methadone treatment often appear at clinics or dosing points with issues unrelated to methadone treatment. The requisite skills to help patients deal with a variety of problems are indispensable.

More commonly, problems arise relating to disputes over program rules, patient behaviour and compliance. Resolving these often requires considerable skill and restraint. In any treatment program there must be constant interaction between clinic staff and patients. How these interactions are managed can have a major impact on treatment outcome.

2 Treatment approaches in Australia

2.3.5 *Induction into substitution treatment*

Methadone

The history of quantity, frequency and route of administration of opioids, findings on examination, corroborative history and urine testing together provide an indication of the level of tolerance a patient has to opioids, but do not predict it with certainty.

A defined period of observation for signs and symptoms of opioid toxicity and withdrawal is a more accurate method of assessing opioid tolerance than history alone. In circumstances where there is doubt about the degree of tolerance, a review of the patient at a time when withdrawal symptoms are being experienced may help to resolve uncertainty about a safe starting dose.

While initial doses of methadone which are too high can result in toxicity and death, inadequate commencement doses may cause patients experiencing withdrawal symptoms to “top up” the prescribed dose of methadone with benzodiazepines or other opioid drugs. This can also have potentially lethal consequences.

The first two weeks of methadone treatment is a high risk period for overdose (Cornish, et al., 2010; Degenhardt, Randall, et al., 2009).

Deaths in the first two weeks have been associated with doses in the range 25-100 mg/day, with most occurring at doses of 40-60 mg/day (R. Humeniuk, et al., 2000).

Deaths during the induction phase of methadone treatment have been related to:

- Concomitant use of other drugs (particularly sedatives such as alcohol and benzodiazepines);
- Inadequate assessment of tolerance;
- Commencement on doses that are too high for the level of tolerance;
- Lack of understanding of the cumulative effect of methadone;
- Inadequate observation and supervision of dosing;
- Individual variation in metabolism of methadone.

LINK

A4.2.1 recommended regimens for induction onto methadone

Buprenorphine

With buprenorphine the aim should be to stabilise patients on an effective dose of buprenorphine as soon as possible. More rapid dose induction (i.e. 12-16mg by day 3) may be associated with better retention in treatment (Amass et al., 2011; Doran, Holmes, Ladewig, & Ling, 2005). However, this needs to be weighed against individual reactions to initial dosing and safety considerations.

The risk of overdose during buprenorphine induction is low (Degenhardt, Randall, et al., 2009), but in patients with high neuroadaptation to opioids the initial dose of buprenorphine may precipitate withdrawal (Clark, et al., 2002; Johnson, et al., 2003).

Buprenorphine precipitated withdrawal typically begins one to four hours after the first buprenorphine dose, is generally mild to moderate in severity, and lasts for up to 12 hours. Administration of the first dose of buprenorphine early in the day provides an opportunity to manage precipitated withdrawal if it occurs.

LINK

A4.2.2 recommended regimens for induction onto buprenorphine

2 Treatment approaches in Australia

2.3.6 Maintenance doses

Methadone

Generally patients receiving a daily dose of 60 mg or more have better treatment outcomes than those receiving less than 60 mg (Faggiano, et al., 2003), in terms of:

- Retention in treatment;
- Unsanctioned opioid use;
- HIV risk-taking behaviour;
- Criminal activity.

Cross tolerance to heroin or other opioids increases as a function of increasing methadone dose and results in blockade of the euphoric effect of concurrent opioid use. A daily methadone dose of 60mg or greater should be sufficient to ensure a substantial level of tolerance to effects of heroin or other opioids in the majority of individuals.

LINK

A4.3.1 Optimising medication dosing regimens

Buprenorphine

Effective maintenance doses of buprenorphine, resulting in reduced heroin use and improved treatment retention, may be achieved with buprenorphine doses in the range of 8 to 24mg/day. Doses of 4mg or less will not be as effective in retaining patients in treatment or reducing heroin use (evidence suggests that such doses produce outcomes that are similar to, or worse than, the outcomes associated with methadone doses of 20mg). Most patients will require at least 12mg daily for effective buprenorphine maintenance treatment, and most patients will be able to be maintained on a dose of around 16mg/day.

Randomised controlled trials comparing buprenorphine doses have found doses of 8mg/day to be significantly more effective than 1mg/day, while doses of 12 mg/day are significantly more effective than doses of 4mg/day in reducing heroin use (Ahmadi, 2002; Ahmadi & Ahmadi, 2003; Kosten, Schottenfeld, Ziedonis, & Falcioni, 1993; Schottenfeld, Pakes, Oliveto, Ziedonis, & Kosten, 1997; Seow et al., 1986). A number of studies have shown a trend for 16mg to be more effective than 8mg daily (W. Ling et al., 1998; Montoya et al., 2004). This is supported by a trend for higher doses of buprenorphine (up to 32mg) to block the effects of other opioids better (Comer, Collins, & Fischman, 2001; Greenwald, 2002; Schottenfeld, Pakes, Ziedonis, & Kosten, 1993; Walsh, et al., 1995). There has been little investigation of the efficacy of daily doses higher than 12mg compared to lower doses, and little is known regarding the nature of adverse events at maintenance daily doses greater than 32mg. Increases in the dose of buprenorphine will not necessarily result in a proportional increase in buprenorphine levels (Harris et al., 2004).

2 Treatment approaches in Australia

Evidence from randomised controlled trials (Amass, Bickel, Crean, Blake, & Higgins, 1998; Amass, Bickel, Higgins, & Badger, 1994; Amass, Kamien, & Mikulich, 2000, 2001; Fudala, Jaffe, Dax, & Johnson, 1990; Johnson et al., 1995; Kuhlman, Levine, Johnson, Fudala, & Cone, 1998; Perez de los Cobos et al., 2000; Petry, Bickel, & Badger, 1999; Schottenfeld et al., 2000) indicates that daily and alternate daily or three-times-a-week dosing are similar in efficacy when doses are adjusted appropriately, although a few of these studies reported a non-significant trend for daily dosing to produce less withdrawal symptoms between doses and less heroin use (Amass, et al., 2000, 2001; Fudala, et al., 1990; Johnson, et al., 1995; Kuhlman, et al., 1998; Perez de los Cobos, et al., 2000; Petry, Bickel, & Badger, 2000; Schottenfeld, et al., 2000).

Takeaways and unsupervised dosing

In general, treatment of opioid dependence with methadone or buprenorphine is based on daily, supervised dosing at a pharmacy or clinic, with access to takeaway doses approved according to individual patient circumstances. The provision of takeaway doses can improve patient engagement in treatment, and promote patient autonomy in the management of their medication and treatment in general, consistent with the principles of chronic disease management. However, there are also potential harms associated with unsupervised and takeaway doses of methadone or buprenorphine, to the patient or others and to the broader opioid treatment program. Hence takeaway doses need to be agreed in a context of mitigation of the risks of harms.

LINK

Takeaways and unsupervised dosing in A4.3.1

A10.4 Criteria for takeaways and unsupervised dosing

Most studies of opioid substitution treatment have been undertaken in a context of supervised dosing with the result that there is very little evidence on the effectiveness of takeaway and unsupervised dosing. However, it is possible to collate the potential harms that can arise from inappropriate use of takeaway doses (see table on the next page).

LINK

Glossary of terms and abbreviations

2 Treatment approaches in Australia

Activity	Safety concerns	Methadone	BPN	BNX
Patient using takeaway dose whilst intoxicated on other drugs.	Further intoxication, sedation, overdose	+++	++	++
Patient consuming a dose after period of several missed doses	Intoxication or overdose (if tolerance has reduced) on recommencing	++	+	+
	Precipitated withdrawal if recommencing BPN/BNX after recent opioid agonist use (e.g. heroin).	-	++	++
Poor medication adherence: (taking higher or lower doses than prescribed)	Intoxication and overdose Increased tolerance	++	+	+
	Reduced treatment effectiveness (e.g. running out of medication early, relapse to other substance use, destabilized other conditions)	++	++	++
Use by non-prescribed routes (injected, intranasal)	Intoxication, overdose (higher peak plasma concentration)	+++	++	+
	Vein damage, infections, BBV	++	+++	++
Intentional or accidental use of opioid medication by person for whom not prescribed.	Intoxication and overdose risk. Particular concern with children and others with low opioid tolerance	+++	++	++
	Opioid related harms, including adverse drug effects, route of administration, economic, legal and psychosocial consequences	++	++	++
Regular use of opioid medication by person for whom not prescribed.	Development of dependence to medication	++	++	++
Illegal activities associated with selling, diverting or possession of medications not prescribed to patient.	Regulatory and legal and consequences	++	++	++
Poor reputation of opioid treatment from misuse of unsupervised medication	Stigma against patients and treatment services	++	++	++
	Reduces attractiveness of treatment to target population, health providers and community	++	++	++

Dilution of takeaway doses of methadone can help to reduce risks associated with injection of methadone syrup, and unintentional use of methadone by persons for whom it has not been prescribed (Humeniuk et al., 2003).

LINK

A10.4 Criteria for takeaways and unsupervised dosing

2 Treatment approaches in Australia

2.3.7 *Adverse effects*

An adverse drug reaction is any undesired or unintended effect of drug treatment. Adverse drug reactions may be predictable on the basis of the drug's known actions, or unpredictable (e.g. allergic drug responses, idiosyncratic drug reactions). It can be difficult to establish the causal agent in allergic reactions. Reported allergies need to be approached with caution because of the potentially serious consequences of severe reactions.

The reported side effects of methadone and buprenorphine are qualitatively similar to those of other opioid drugs (see table). Most people who have used heroin or other opioids will experience few side effects.

Side effect	Common causes	Things you can do
Feeling drowsy after taking dose	• Dose too high	Lower the maintenance dose and review other medications the patient may be taking
	• Other drug use (legal or illegal)	Review use of sedative and other drugs affecting cognition
Withdrawal symptoms maximal before next dose	• Dose too low	Raise maintenance dose
	• Changes in legal or illegal drugs that patient may be using	Review other drugs patient is taking
Withdrawal precipitated by buprenorphine dose	Occurs early in treatment (or after absence from treatment) when buprenorphine dose administered soon after opioid use (e.g. heroin, methadone, morphine)	Transient effect. Aim to prevent by patient education. Delay buprenorphine dose until patient experiencing opioid withdrawal. Discourage use of on-top heroin.
Headache	• Common in first week of buprenorphine treatment	Side effect is transient and generally mild. Consider aspirin or paracetamol.
	• Other causes of headache	Consider other causes
Nausea	Common early in treatment, particularly if buprenorphine dose high	Side effect usually transient (days). Avoid rapid dose increases. Consider dose-reduction if persistent.
Constipation	All opioids do this. Will be made worse by lack of dietary fibre, fluid intake or exercise.	Encourage fibre intake (fruit, cereals, vegetables), fluids, and regular exercise. Stimulant laxatives if necessary
Weight gain, particularly for women	• Fluid retention caused by opioids – more likely on high doses	Lower dose
	• Eating more while in treatment; high salt intake	Reduce fat and salt in diet, exercise regimen
Poor sleep	• Dose too low and causing withdrawal at night	Review maintenance dose and review other medications
	• Dose too late at night, causing stimulation at time of peak effects	Follow sleep hygiene recommendations
	• Other drugs (particularly stimulants in the evening, such as coffee, nicotine, amphetamines)	

2 Treatment approaches in Australia

Side effect	Common causes	Things you can do
Poor sleep (cont)	• General anxiety or irregular sleep pattern	Follow sleep hygiene recommendations
	• Depressive illness	
	• Central sleep apnoea	Assess and consider referral
Amenorrhoea or oligomenorrhoea	• All opioids can do this	Periods may return after cessation of heroin use, or following withdrawal from opioids.
	• May be related to lifestyle, stressors, poor diet, and general poor health	• Address other causes
Lowered sex drive	• More common with a high dose through effect on sex hormones • Can be many other psychological factors (such as anxiety, poor relationship with partner, etc.)	• Review dose • Consider investigation for opioid-induced hypogonadism
Dental problems	• All opioids reduce saliva flow • Poor diet, dental hygiene	Encourage oral hygiene, dental floss and use of sugar free gum. Dental check-up. Reduce intake of sugary drinks and sweet food.

Table: Common side effects with opioid substitution treatment.[17]

Once on a stable dose, tolerance develops until cognitive skills and attention are not impaired.

Studies have identified insomnia, sweating, painful joints and bones, constipation and craving as the most common complaints of methadone maintenance patients. These complaints are experienced to some extent, by 40-50% of patients and to a severe degree by approximately 20%. Around one-third may experience withdrawal symptoms due to the methadone dose not “holding” for the full 24-hour period (Dyer & White, 1997). A three-year prospective study in the USA of persons entering treatment with methadone identified increased perspiration as the only side effect that persisted (Kreek, 2000). This study also identified adult onset diabetes, obesity and hiatus hernia as being more common in the methadone-maintained population compared to untreated heroin users matched for age and years of addiction. In contrast, in the heroin-addicted populations, cutaneous ulcers, skin infections, bacterial endocarditis, burns and gunshot wounds were more common. Many specific components of immune function are severely compromised in heroin addicts. During substitution treatment with methadone there is a steady and continuing improvement, with eventual normalisation of these components (Kreek, 2000).

[17] Modified from Dunlop et al., (1996). *Getting through methadone withdrawal*. Turning Point Alcohol & Drug Centre: Fitzroy, Melbourne.

2 Treatment approaches in Australia

Symptoms of constipation, sexual dysfunction and occasionally increased sweating can continue to be troubling for the duration of substitution treatment with methadone (Kreek, et al., 2010). People rarely develop tolerance to the constipating effects of opioids and patients on substitution treatment may experience chronic constipation. Encourage the consumption of plenty of fruits and vegetables and non-alcoholic fluids each day, and stimulant laxatives if necessary. Central sleep apnoea can be a side effect of methadone and is exacerbated by the use of night sedation (Teichtahl, et al., 2001; Zutler & Holty, 2011).

In large, multicentre trials of buprenorphine maintenance treatment, the most common adverse event (reported in over 30% of patients) has been opioid withdrawal symptoms, and these reports have been most common in patients on low doses of buprenorphine (e.g. 1mg daily). Other commonly reported adverse events reported by the manufacturer are headache, constipation, insomnia, asthenia, somnolence, nausea, dizziness, and sweating, occurring in less than 10% of patients, particularly with doses of buprenorphine greater than 8mg/day.

Elucidate the cause of any significant lethargy. Dose of medication, particularly methadone, may need to be reduced.

For excessive sweating, try reducing the dose but this may not alleviate the symptoms. Sweating can also be a prominent symptom in withdrawal – careful history taking and observation of the patient prior to dosing may be necessary to assist in making the distinction.

Buprenorphine may be the optimal choice for those with renal dysfunction requiring maintenance treatment (A. R. Lingford-Hughes, et al., 2012).

Overdose

The major hazard associated with substitution treatment is the risk of overdose, particularly with methadone. Induction onto methadone maintenance treatment is more hazardous than induction onto buprenorphine|★★|. An analysis of 42,676 entrants to opioid pharmacotherapy treatment in New South Wales during the period 1985 to 2006, identified only one death during induction onto buprenorphine. This related to a crude mortality rate of 2.5 per 1000 person years, compared to 26.3 per 1000 person years for methadone induction during the same period (Degenhardt, Randall, et al., 2009).

Methadone

The risk of methadone overdose is particularly high at the time of induction to MMT and when methadone is used in combination with other sedative drugs. The relatively slow onset of action and long half life mean that methadone overdose can be highly deceptive and toxic effects may become life threatening (overdose) many hours after ingestion. Because methadone levels rise progressively with successive doses during induction into treatment, most deaths in this period have occurred on the third or fourth day of treatment.

LINK

2.3.5 Induction into substitution treatment

2 Treatment approaches in Australia

Signs and symptoms of methadone overdose	
Pinpoint pupils	Nausea
Dizziness	Feeling intoxicated
Sedation/nodding off	Unsteady gait, slurred speech
Snoring	Hypotension
Slow pulse (bradycardia)	Shallow breathing (hypoventilation)
Frothing at the mouth (pulmonary oedema)	Coma

Note: Symptoms may last for 24 hours or more. Death generally occurs from respiratory depression.

Most deaths during stabilisation on methadone have involved other drugs, in particular, alcohol, benzodiazepines and antidepressants. Patients should be warned of the risks associated with using other drugs with methadone.

Death during methadone induction often occurs at home during sleep, many hours after peak blood methadone concentrations have occurred. Typically overdose occurs around the third or fourth day of methadone induction.

Given that many deaths occur during sleep, administration of methadone in the morning will ensure peak methadone concentrations occur when patients are normally awake and other people may be around if overdose should occur.

Naloxone promptly reverses opioid induced coma. However, a single dose of naloxone will wear off within one hour leaving patients at risk of relapse into coma due to the long lasting effects of methadone (Kreek, et al., 2010). Monitoring of the person's clinical state is important. Transfer to hospital is appropriate for determination of the need for prolonged infusion of naloxone.

Patients who are thought to have taken a methadone overdose require prolonged observation.

Family members should be warned that deep snoring during induction to treatment could be a sign of dangerous respiratory depression and should be reported to the prescriber. Heavy snoring during maintenance treatment may be associated with sleep apnoea and should also be reported.

Buprenorphine

The risk of lethal overdose in an opioid-tolerant individual on buprenorphine is substantially less than that associated with the use of other opioid medications, such as methadone (Gaulier, Charvier, Monceaux, Marquet, & Lachatre, 2004; Walsh, et al., 1995). This is due to the ceiling dose response effects of buprenorphine.

While overdose on buprenorphine is relatively uncommon, there is a greater risk when it is combined with other sedative drugs, such as alcohol, benzodiazepines, barbiturates, tricyclic antidepressants and major tranquillisers. Deaths due to the combination of buprenorphine and other sedatives have been reported (Faroqui, et al., 1983; Forrest, 1983; Papworth, 1983; Sekar & Mimpriss, 1987).

2 Treatment approaches in Australia

An opioid-naive individual may overdose with a high dose of buprenorphine. The poor bioavailability of buprenorphine when taken orally reduces the risk of serious effects from accidental intake by children.

Buprenorphine has affinity for mu opioid receptors and is not easily displaced by the antagonist, naloxone. In the event of overdose of buprenorphine, very high doses of naloxone may be required to partially reverse its effects. Cases have been reported in which naloxone in doses of 10 to 35 mg were required (Eissenberg et al., 1996; Gal, 1989; Knape, 1986; Quigley, Bredemeyer, & Seow, 1984; T. S. Rosen & Johnson, 1982; Thorn, Rawal, & Wennhager, 1988), while in other cases doses of 2mg or less were reported to be effective in reducing respiratory depression (Boyd, Randell, Luurila, & Kuisma, 2003).

Because of the uncertain response to naloxone, prolonged ventilator support may be required in overdoses involving buprenorphine. In the event of depression of respiratory or cardiac function:

1. re-establish patient airway;
2. begin assisted or controlled ventilation with oxygen, and apply intravenous fluids, vasopressors and other supportive measures as indicated;
3. the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose.

Sexual dysfunction

Sexual dysfunction in men appears to be related to lower-than-normal serum levels of testosterone. In women sexual dysfunction is primarily related to interference with the normal cyclic production of LH and FSH, possibly due to elevated production of prolactin (R. T. Brown & Zueldorff, 2007; Kreek, et al., 2010). The clinical significance of sexual dysfunction lies in the potential to lead to decreased compliance with therapy and to interfere with the known benefits of opioid substitution treatment. Switching to buprenorphine may help, with a single study finding that buprenorphine had less effect on testosterone levels in males and was associated with a lower prevalence of sexual dysfunction than methadone (R. T. Brown & Zueldorff, 2007).

In the case of libido dysfunction, mental and emotional health should be investigated in addition to hormonal assays. Medications other than opioid substitutes should also be reviewed. Erectile dysfunction is more likely to have organic or iatrogenic etiology. Mental and emotional health, other medications and smoking may be contributing factors (R. T. Brown & Zueldorff, 2007).

Nearly 50% of women experience menstrual irregularity while on MMT. The effect appears to be dose-related and appears to decline over time (R. T. Brown & Zueldorff, 2007).

Therapeutic options include replacement of abnormally low testosterone, transfer to buprenorphine or a reduction in the dose of medication (but this needs to be balanced against the risk of return to uncontrolled opioid use).

2 Treatment approaches in Australia

Prolongation of QTc interval

The QTc interval normally varies depending on heart rate, age and gender. The QTc interval may be influenced by electrolyte balance, medications, and ischaemia. There is evidence that QTc interval prolongation is associated with increased risk of cardiovascular comorbities, including sudden cardiac death, with the degree of risk increasing with age (Moss, 2006; Straus et al., 2006) and a range of other risk factors (Martin et al., 2011).

QTc interval prolongation is evident in 10-15% of people on MMT, but not buprenorphine (Anchersen, Clausen, Gossop, Hansteen, & Waal, 2009; Roy et al., 2012; Stallvik et al., 2013). Although the greatest prolongation of QTc interval has been observed (Martell, Arnsten, Ray, & Gourevitch, 2003) in men receiving higher methadone doses (110 to 150mg) there is no clear evidence on the relationship between dose and QTc interval.

A number of other factors, in addition to methadone, appear to be important in QTc prolongation in opioid dependent people, including:

- congenital long QTc syndrome (family history, including family history of unexplained sudden death);
- cardiac abnormalities (infective endocarditis, valvular lesions, cardiomyopathy, ischaemia);
- other drugs, including medications (atypical antipsychotics, tricyclics antidepressants, antiretroviral agents – link to drug interactions below and appendix 3) and unsanctioned substance use (alcohol, caffeine, amphetamines, cocaine and other stimulants, tobacco);
- electrolyte or metabolic disturbances (including systemic infections, hypokalaemia as may occur with vomiting and diarrhoea associated with alcohol or opioid withdrawal).

LINK
A4.4.4 Recommended approach to prolong-ation of QTc interval

Drug interactions

Methadone and buprenorphine exert additional sedative effects when used in conjunction with other sedating medications. These include other opioids, benzodiazepines, alcohol, tricyclics antidepressants, sedating anti-histamines, and major tranquillisers.

As methadone has a more marked respiratory depressant effect, the interaction between methadone and sedative drugs is more significant. However, the combination of buprenorphine with benzodiazepines, alcohol and other sedatives has also been associated with fatal overdoses.

LINK
A4.4.5 Drug interactions
Overdose in 2.3.7

Other drug interactions may arise from effects on liver enzymes, either increasing or decreasing metabolism of methadone or buprenorphine, or the medication being used in combination with methadone or buprenorphine.

The most significant interactions are with drugs that inhibit the activity of the cytochrome system (particularly cytochrome p450-3A) which results in decreased metabolism of methadone or buprenorphine and consequently increased blood levels (Eap, et al., 2002). Such interactions are most significant with methadone due to the potential for overdose.

2 Treatment approaches in Australia

Conversely, drugs that induce the metabolism of methadone and buprenorphine may result in decreased blood concentrations and hence withdrawal symptoms.

Medications that have the potential to cause prolongation of the QTc interval may be contraindicated for use in combination with methadone and buprenorphine.

LINK
Prolongation of QTc interval (page 108)

Further information on the interaction of prescription medications with methadone and buprenorphine is available from www.opioiddruginteractions.com/. A list of medications that are known to, or may potentially cause clinically significant interactions with methadone and buprenorphine are listed in Appendix 3.

LINK
Appendix 3: Drug interactions

2.3.8 Completing substitution treatment

When to end treatment

Research evidence indicates that treatment programs with defined timeframes and requirements for abstinence are less effective than those with more flexible arrangements (Bell, Chan, & Kuk, 1995; Sees et al., 2000). It is also important that adequate doses of methadone or buprenorphine are prescribed as inadequate dosing is associated with increased risks of dropout from treatment and recommencement of uncontrolled drug use (Faggiano, et al., 2003) with all the attendant harms.

Opioid substitution treatment is a maintenance intervention. It is not a time-limited treatment. Any notion of opioid substitution treatment as an effective time-limited treatment with the expectation of 'cure' is not supported by the research literature (Kreek, 2000). Rather the evidence suggests that the longer a patient remains in treatment, the more likely they are to do well and, in the longer term, the more likely they are to do well after ceasing substitution treatment (Ball, Lange, Myers, & Friedman, 1988; Gossop, 2011; Hubbard, Craddock, & Anderson, 2003; Kakko, Svanborg, Kreek, & Heilig, 2003). It is important to note that people who drop out of treatment, particularly in the first year, have a very high rate of relapse to heroin or other opioid use (Magura & Rosenblum, 2001).

The findings of multiple observational studies indicate that it is a combination of treatment duration and behaviour change (ceasing heroin use, stable relationship, employment) during treatment which predicts positive post treatment outcomes (WHO, 2009).

A cross-sectional survey of 145 patients (61% methadone, 39% buprenorphine) found that 71% had made previous attempts to come off treatment, and 23% had achieved abstinence for at least three months (Winstock, Lintzeris, & Lea, 2011). The emphasis on keeping people in treatment is at odds with the strong wish of many patients to come off treatment, which is compounded by perceptions in the wider community that methadone perpetuates dependence (Winstock, et al., 2011). The issue of coming off treatment is important to many patients and should be discussed regularly throughout treatment. The fear of being stuck on methadone, and the failure of services to address withdrawal concerns, may contribute to patients seeking short-term treatment episodes and avoiding higher methadone doses, which in turn may compromise the goals of opioid substitution treatment (Winstock, et al., 2011).

2 Treatment approaches in Australia

Process of cessation

The majority of terminations are initiated at the request of the patient, for various reasons around lifestyle, cost and time demands of OST, and perceptions and attitudes directed towards OST.

However, the final decision to discontinue opioid substitution treatment is the responsibility of the prescribing medical practitioner in consultation with the patient. Dose reduction should be made in consultation with the patient. In general, the slower the rate of reduction, the less severe are the effects of withdrawal. Continued reduction of dose producing or precipitating physical or psychological distress for the patient is usually counter-productive.

The likelihood of premature withdrawal from substitution treatment is reduced by ensuring patients are well-informed about the maintenance program.

Dose reduction from opioid substitution treatment with the ultimate aim of achieving a period of abstinence from opiates needs to be planned and delivered within a period of stability and sustained motivation. Patients usually benefit from psychosocial support, including counselling, at this time.

Before commencing a reduction in medication dose, the clinician should assess the patient and determine their motivation, psychosocial stability, current alcohol and drug use, expectations, source of support, concerns and aftercare plans. A treatment plan for withdrawal should be developed, including the pattern of dose reduction, and preparation for withdrawal (e.g. removing paraphernalia, informing significant others, avoiding stressors etc). Information should also be provided to the patient about the nature and severity of withdrawal from the substitute medication, and of the possibility of a return to medication-assisted treatment should they find that continuing withdrawal is placing them at risk of relapse.

Increased supportive counselling as well as information and education should be available for patients withdrawing from opioid substitution treatment. There may be a role for other medication, such as clonidine, non-steroidal anti-inflammatory drugs, anti-emetics, or anti-diarrhoeal agents for symptomatic relief.

LINK

A4.6 Cessation of substitution treatment

Methadone

During voluntary methadone withdrawal, a flexible approach to dose reduction is advised and it should be made in consultation with the patient. In general, successful completion of withdrawal from methadone maintenance treatment is more likely if undertaken over a longer period. A recent study of a cohort of patients receiving methadone treatment in the province of British Columbia, Canada, found that those who successfully completed withdrawal were likely to have had a longer reduction period (12-52 weeks, compared to less than 12 weeks), with a more gradual, stepped tapering schedule involving a dose decrease in only 25-50% of the weeks of taper (Nosyk et al., 2012).

2 Treatment approaches in Australia

Buprenorphine

Research evidence regarding the nature and severity of withdrawal following cessation of buprenorphine maintenance treatment remains limited. Furthermore, many of the early studies of buprenorphine withdrawal relied on observers' assessments of objective withdrawal signs, which can produce a significantly different view to subjective assessments by patients of withdrawal severity (Kosten, Rounsaville, & Kleber, 1985). The symptoms and signs of withdrawal from buprenorphine are qualitatively similar to withdrawal from other opioids. Typically, the withdrawal syndrome following the abrupt cessation of long-term buprenorphine treatment emerges within three to five days of the last dose, and mild withdrawal features continue for up to several weeks. The withdrawal syndrome on cessation of buprenorphine may be milder than withdrawal from heroin, morphine and methadone (Amass, Bickel, Higgins, & Hughes, 1994; Cami, Gilabert, San, & de la Torre, 1992; Horgan, 1989; Jasinski, 1981; Jasinski, et al., 1982; Mello & Mendelson, 1980; Mudric, et al., 1998; Resnick et al., 1992; San, et al., 1992).

As with methadone, studies suggest that more gradual tapers of dose are more effective for cessation of buprenorphine maintenance than more rapid dose reduction regimens (Amass, Bickel, Higgins, & Hughes, 1994; Becker, Strain, Bigelow, Stitzer, & Johnson, 2001). More rapid dose reduction may be considered in those who only had a recent brief period of treatment or when circumstances make rapid dose reduction desirable. More rapid dose reduction when conducted on an outpatient basis should only be conducted when there is significant support and opportunity for review.

Aftercare and follow-up

At the end of substitution treatment there should be some continued follow-up assistance (i.e. aftercare). The form of aftercare can be 'booster sessions' to maintain skills etc, learnt in treatment, or it can be simple support and monitoring of progress as the patient reintegrates into the community.

The patient should understand the importance of continued contact with the counsellor or medical practitioner and should be made to feel that contact is not only acceptable but expected.

Longer duration and greater intensity of pre-treatment opioid use is associated with an increased probability of relapse to opioid use after leaving treatment.

The likelihood of a patient maintaining abstinence after leaving treatment is increased in people who have established drug-free social supports, are in stable family situations, employed, and with good psychological strengths (Simpson, Joe, Greener, & Rowan-Szal, 2000).

There is evidence from RCTs that structured aftercare (compared with assistance on request) reduced the risk of relapse, self-reported crime and helped unemployed patients find work.

Supportive care should be offered for at least six months following cessation of substitution treatment. Self-help groups such as Narcotics Anonymous and SMART Recovery may be beneficial.

LINK

2.5.4 Psychosocial support

2 Treatment approaches in Australia

2.4 Relapse prevention: Naltrexone maintenance treatment

Psychological conditioning is considered to play a large role in the initiation and continuation of drug use, with the euphoric effects of drugs acting as a strong positive reinforcement for further use. Positive reinforcement may be balanced to some extent by negative consequences of drug use, but the negative consequences (health problems, unemployment, financial and legal difficulties) tend to be more remote from the act of drug use, and less certain (L. Gowing, et al., 2001; T. K. Tucker & Ritter, 2000).

Relapse prevention or rehabilitation programs are designed to change the behaviour of patients to enable them to regain control of their urge to use alcohol and other drugs. Some medications help support relapse prevention interventions. These medications control craving and withdrawal symptoms, and block or modify responses to drug use. In the case of opioid dependence, the primary medication used for relapse prevention is naltrexone. Naltrexone is an opioid antagonist which attenuates the effects of heroin and most other opioid drugs for approximately 24 hours after each 50mg dose (WHO, 2009). By preventing euphoric effects, naltrexone helps to extinguish drug-seeking behaviour and craving.

The rationale for using naltrexone in relapse prevention is that the patient knows that taking naltrexone blocks the effects of opioid drugs. Detoxified opioid users have described naltrexone as being a form of “insurance”, a protection against a sudden temptation to use opioid drugs. Clinical experience indicates that people who take naltrexone in the hope that it will stop them wanting to use opioid drugs, or will maintain their motivation to remain abstinent, tend to be disappointed. Naltrexone should be seen as a medication which may help motivated patients to remain abstinent, rather than a drug which reduces patients’ desire to use heroin or other opioid drugs. Furthermore, it should be remembered that “motivation” to remain drug-free can be very variable over time. It is common that people in crisis express a strong intention to become and remain drug free, but within a relatively short time such determination disappears.

2.4.1 Effectiveness of naltrexone treatment

A systematic (Cochrane) review found no significant difference in treatment retention or abstinence for people treated with naltrexone with or without adjunct psychosocial therapy, compared to placebo or psychosocial therapy alone (Minozzi et al., 2011) |★★|. However, the findings were limited by low rates of retention in studies, and the small number of comparable studies. Australian experience indicates that this treatment has limited acceptability and rates of dropout from treatment are relatively high. In a study in Melbourne (T. Tucker, Ritter, Maher, & Jackson, 2004) only 30% of people screened entered naltrexone treatment, and only 30% of those remained in treatment for the full 12 weeks of the study.

The limited evidence available suggests that, in dependent opioid users who have withdrawn from opioids, those who take naltrexone are less likely to use heroin or engage in criminal activity than those who do not take naltrexone. Retention in treatment is generally likely to be lower than opioid agonist maintenance therapy; nevertheless, in those patients who have withdrawn from opioids and are motivated to cease opioid use completely, relapse prevention efforts with naltrexone are likely to be superior to those without naltrexone (WHO, 2009).

2 Treatment approaches in Australia

Naltrexone may be more effective when family members are involved in the treatment or directly observe the patient taking naltrexone. Clinical experiences with naltrexone vary considerably between countries, with some countries finding levels of retention similar to opioid agonists and others finding very poor rates of retention. It is possible that cultural and social differences could result in variable efficacy and acceptability of naltrexone treatment. Clinical experience suggests that naltrexone may be more effective in patients who have strong, external motivating factors to support abstinence from opioid use, for example, professionals at risk of losing their employment (Merlo, Greene, & Pomm, 2011), or patients who have come before the courts and risk incarceration (WHO, 2009). People whose family networks have remained intact and who have a family member or close friend to supervise their use of naltrexone are also good candidates for naltrexone maintenance treatment.

Initial studies indicate that, compared with usual aftercare following inpatient treatment, naltrexone implant was associated with significantly fewer days of heroin use in a 6-month follow-up period (Kunoe et al., 2009). A total of 667 people were assessed for eligibility for this study; 480 did not meet inclusion criteria and 131 refused to participate. The study was based on 56 participants who were randomised to either naltrexone implant or treatment as usual. This emphasises that treatment with naltrexone implant may be appropriate for only a minority of dependent opioid users. Another study found improved retention in treatment for injectable sustained-release naltrexone compared with placebo, and higher retention with higher dose, but no effect on abstinence (Comer et al., 2006). However, neither implant nor depot preparation are registered for therapeutic use in Australia.

People receiving naltrexone maintenance treatment should have access to a comprehensive range of psychosocial treatments and supports. With more intensive supportive treatment, and with new methods of delivering naltrexone, it is thought that the effectiveness of treatment with this medication can be improved. However, at this time the available evidence suggests only very modest efficacy of naltrexone in relapse prevention for opioid dependence (Adi et al., 2007; Minozzi, et al., 2011).

2.4.2 Initiating naltrexone treatment

Commencing naltrexone following buprenorphine maintenance treatment

Due to the pharmacological properties of buprenorphine (Sigmon, et al., 2012), the transition from buprenorphine to naltrexone is easier than the transition from full opioid agonists (methadone, heroin, morphine).

When commencing naltrexone following buprenorphine maintenance treatment, naltrexone should be delayed for 5-7 days after the last buprenorphine dose to minimise the risk of withdrawal symptoms. Doses of naltrexone taken earlier than this are likely to induce some withdrawal symptoms depending on the buprenorphine doses in the last few weeks and the timing of the first naltrexone dose (Eissenberg, et al., 1996; Kosten, Morgan, & Kleber, 1991; M. Rosen & Kosten, 1995; Umbricht et al., 1999).

LINK

A5.4 Recommended approach to initiation of naltrexone maintenance treatment

2 Treatment approaches in Australia

Withdrawal symptoms associated with the first dose of naltrexone typically commence 90 minutes to 4 hours after the first naltrexone dose, peak around 3-6 hours after the naltrexone dose, and generally subside in severity within 12-24 hours. The withdrawal is frequently experienced as moderate to severe at its peak. Subsequent doses of naltrexone produce considerably less severe withdrawal discomfort. Patients should be prepared in advance for the increase in withdrawal severity, the role of medications, and the risks of using heroin or other opioid drugs to overcome the withdrawal symptoms.

2.4.3 Dose and duration of treatment

The usual maintenance dose of naltrexone is 50mg/day. However, 25mg daily produces adequate blockade of opioid receptors, and may be a satisfactory dose in patients who experience side effects from 50mg/day.

The optimal duration for treatment with naltrexone is unknown. However, it is known that treatment for dependence is a long-term process, and there is still a substantial risk of relapse to heroin dependence for 2-3 years after last use of heroin. The optimal period of treatment will be different for different patients and advice about how long to take naltrexone should take into account lifestyle changes, environmental risk factors, and craving.

2.4.4 Supportive care for patients on naltrexone

Intensive follow-up is a critical component of optimising the benefits of naltrexone treatment. The practitioner performing induction onto naltrexone should review patients, or arrange for a suitably qualified health professional to review them, on two occasions during the first week after induction. Thereafter clinical reviews should be conducted weekly during the first month of treatment.

There are many approaches to the delivery of supportive care. These include:

- medical monitoring – regular review with the prescribing doctor, with monitoring of compliance, review of drug use, sometimes with urine testing to confirm self-report;
- counselling – regular scheduled counselling sessions have frequently been used;
- supervised dosing – a family member or friend supervises the daily administration of naltrexone, sometimes administering the tablet crushed to minimise the risk of the patient spitting it out;
- self-help groups may be a valuable adjunct to people trying to maintain abstinence.

LINK

2.5.4 Psychosocial support.

It is important to remember that while families are often keen to be involved in a patient's care on naltrexone, practitioners must obtain each patient's consent to involve family or discuss treatment with them. Remember that every family is different and that adverse family dynamics can contribute to a person's drug use. While most families try to support family members who stop opioid use, a person ceasing opioid use can sometimes lead to considerable family tension. Sensitive handling of such changes could be important in reducing the risk of relapse, including ensuring that the expectations of the patient and their family are realistic.

2 Treatment approaches in Australia

Many people taking naltrexone are keen to engage in some form of counselling, and practitioners who do not feel they have the skills or time to spend in counselling patients should refer patients who express a wish for counselling.

2.4.5 Adjunct pharmacotherapies

There is at this time no evidence to support the routine use of drugs such as antipsychotics, benzodiazepines and anticonvulsants during naltrexone treatment (Bisaga et al., 2011).

Antidepressants

Many dependent opioid users experience dysphoria at treatment presentation, upon completion of withdrawal, and during the induction phase of naltrexone.

- The dysphoria usually resolves within weeks.
- Antidepressants are indicated if there is a diagnosis of depression, as indicated by features more substantial than dysphoria, such as suicidal ideation, anhedonia, sleep disturbance, and weight change.
- Although it has been suggested that use of antidepressants (SSRIs) improves outcomes in unselected naltrexone patients, the weight of evidence does not support routine use of SSRIs in conjunction with naltrexone.

Symptomatic medications

There may be a role for the use of symptomatic medications in the first few days of naltrexone treatment to address ongoing withdrawal symptoms. Recommended medications include metoclopramide for nausea and vomiting, hyoscine butylbromide for abdominal cramps, NSAIDs for joint aches, benzodiazepines for agitation/insomnia, and non-opioid anti-diarrhoeals for diarrhoea.

2.4.6 Undesirable effects and consequences

Although major adverse events are very rare, side effects of naltrexone are common, but tend to be mild and transient, improving with time.

Side effects reported by more than 10% of patients include:

- difficulty in sleeping;
- loss of energy;
- anxiety;
- abdominal pain;
- nausea and vomiting;
- joint and muscle pain; and
- headache.

The greatest problem associated with naltrexone treatment is the increased risk of death from overdose in patients who return to opioid use after being treated with naltrexone.

2 Treatment approaches in Australia

Patients often cease taking naltrexone with the intention of using opioids again, and when they do so it is difficult for them to assess the dose of opioids to use. Because the effects of naltrexone take time to wear off, in the space of 12 hours, the same dose of opioid can be blocked or can be fatal. This may result in higher rates of unintentional opioid overdose in people ceasing naltrexone therapy (WHO, 2009).

Increased risk of death for those patients who return to opioid use after naltrexone treatment is thought to be primarily due to loss of tolerance to opioids. An increase in the risk of death by overdose occurs in any recently detoxified group of formerly heroin dependent patients, including people within 12 months of leaving methadone treatment (Zanis & Woody, 1998). After discontinuing naltrexone, a dose of heroin or other opioid drug which the user had been accustomed to inject during their last period of addiction may now prove fatal.

The experience with naltrexone indicates that there are few serious adverse reactions, other than the precipitated withdrawal, which occurs when the drug is administered to someone who is not opioid free.

Although some years ago it was noted that high doses of naltrexone administered to morbidly obese subjects resulted in transaminase elevations, subsequent experience with use of naltrexone in alcohol dependence has found hepatotoxicity to be rare (Croop, Faulkner, & Labriola, 1997).

2.4.7 Promoting medication compliance

Naltrexone does not cause dependence and for most people its side effects are minimal. There are no symptoms following abrupt cessation of naltrexone. As a result, compliance with medication is problematic.

Naltrexone is reported to be most effective in patients who are highly motivated with good social support and who take the drug as part of a comprehensive occupational rehabilitation program, behavioural contract, or other compliance enhancing process.

Supervised dosing involving a supportive parent, partner or friend may, for some patients, improve compliance with naltrexone treatment.

Contingency management in conjunction with naltrexone may increase treatment retention and compliance. There is also interest in the use of preparations with a longer duration of action than oral naltrexone, including depot and implant forms of naltrexone. Currently there is very limited evidence on the effectiveness of these preparations in the treatment of opioid dependence.

Clarification should be sought as to whether the patient wants to enter into an arrangement in which his/her taking of naltrexone is supervised. This may improve compliance with treatment. Currently several programs encourage patients to involve a significant other (“carer”) to supervise the daily taking of naltrexone, and this may improve compliance and treatment outcomes. Research has demonstrated that treatment with naltrexone is more effective in highly supervised settings such as prisoners on probation (Brahen, Henderson, Capone, & Kordal, 1984), or medical practitioners under the supervision of medical boards (Merlo, et al., 2011; Washton, Pottash, & Gold, 1984). Whether these findings can be extended to having family members or friends as carers remains to be determined.

2 Treatment approaches in Australia

2.5 Adjunct therapies

Assessment of the effectiveness of adjunct psychosocial interventions with pharmacotherapy is complicated by the diversity of psychosocial interventions. There is no clear evidence of enhancement of agonist maintenance treatments by structured psychosocial treatments (L. Amato, et al., 2011b) and methadone even without regular counselling is associated with significant reductions in risk behaviours in the first few months of treatment (Gruber, Delucchi, Kielstein, & Batki, 2008; S. M. Kelly, Schwartz, O'Grady, Gandhi, & Jaffe, 2012). However, overcoming alcohol or other drug dependence entails substantial social and lifestyle adjustments. The provision of psychological and supportive interventions to encourage behavioural and emotional change is important to the overall treatment process (L. Gowing, et al., 2001). Psychological interventions offer formal structured counselling approaches with assessment, clearly defined treatment plans and goals and regular reviews. Informal approaches may involve advice and information, drop-in support and informal counselling (UNODC, 2003).

Psychological interventions may be provided as the major component of alcohol and other drug treatment, or may be provided in conjunction with substitution treatment or other therapies. Psychological interventions help patients to identify and address the reasons for drug use, the negative consequences of their drug use, and the benefits associated with stopping drug use. Identification and development of skills to prevent relapse are also a focus of psychological interventions.

Through these approaches psychological interventions support the process of lifestyle adjustment, help to reduce risk behaviour, and the development of skills to cope with factors that could trigger drug use, or to prevent an occasional lapse becoming a full-blown relapse to regular alcohol or other drug use (L. Gowing, et al., 2001).

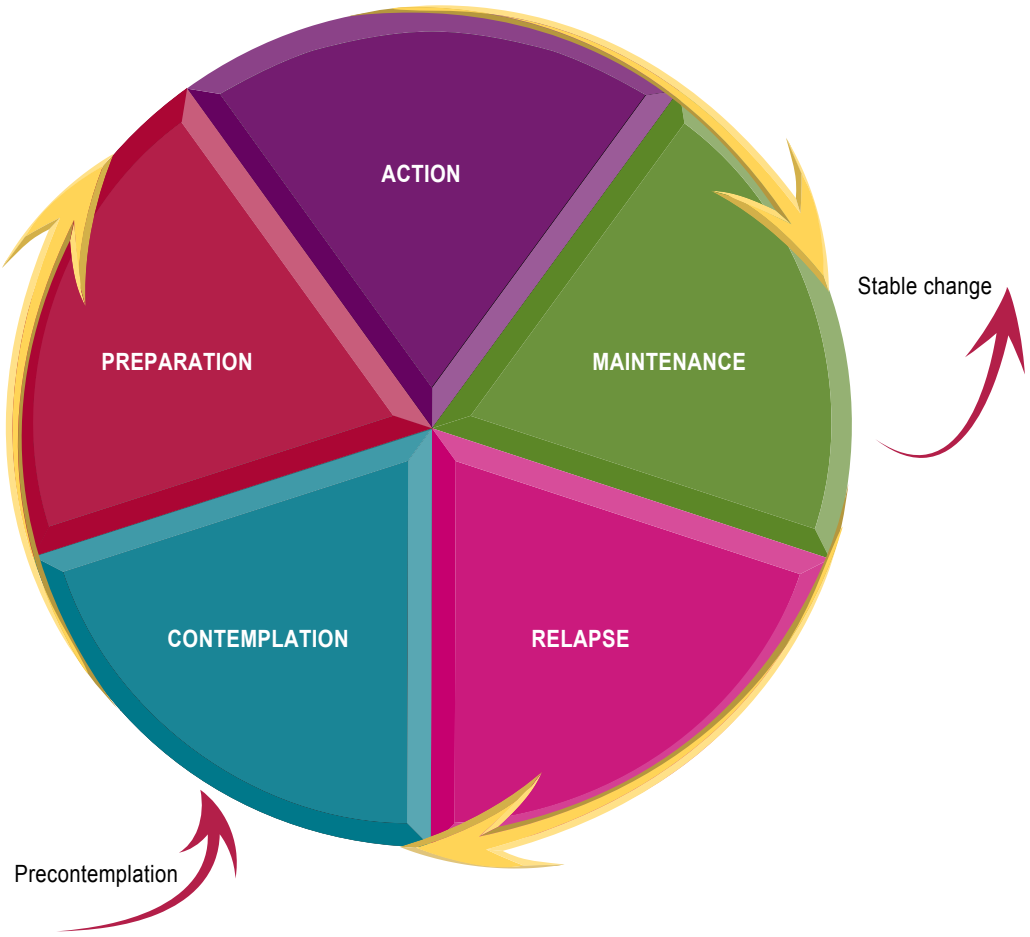
2 Treatment approaches in Australia

2.5.1 Psychological Factors in Treatment

Stages of change

The 'stages of change' model (Miller & Rollnick, 1991; J. O. Prochaska, DiClemente, & Norcross, 1997) is a useful model in understanding of the processes involved behaviour change. The model is based on the concept that individuals (may) pass through a number of stages during behavioural change (Figure 4).

Figure 4: Stages of change



2 Treatment approaches in Australia

Motivation to change is not a 'fixed' state in a person, but rather is subject to many forces including the intervention of health workers. The health worker can assist patients to move from one stage to the next and to learn from unsuccessful attempts to control their drug use.

Pre-contemplation stage

Not all drug users want to stop using drugs. In the pre-contemplation stage, drug users will not have allowed any concerns they may have about their drug use to influence their actions. They will often not immediately recognise problems they are having as resulting from their drug use.

During pre-contemplation the user perceives the benefits of drug use as outweighing the disadvantages, and the disadvantages of change outweigh the advantages. Family, friends, health and social workers may be concerned about some consequences of the person's drug use, but the drug user may accept this as collateral damage.

Commonly, there is resistance to 'action oriented interventions' and explanations about how to 'give up', but relevant information about risks, and how to avoid or minimise them, may be well received. For example, a heroin user may be keen to get advice on how to avoid overdose and blood-borne viruses.

Motivational interviewing is an appropriate technique to help users not contemplating change explore the advantages and disadvantages of current patterns of drug use.

Contemplation stage

The person has realised that their drug use is doing harm and is weighing up the benefits and the costs of continuing to use. The balance of costs and benefits begin to shift, although there is still ambivalence about change.

This ambivalence is best explored using motivational interviewing.

Preparation stage

The balance has shifted. The person is preparing to take action and has confidence in their capacity to change. Change is seen as worthwhile. This is often a planning stage. Goal setting, identifying internal and external supports/ resources and identifying strategies to support change can help.

Action stage

The person is taking steps to change. Support and specific skill training can be provided.

Review initial reasons that led to the decision to change. The person is implementing strategies to change their drug use pattern. They usually spend the least time in this stage as they are either waiting to enter treatment, relapsing and returning to thinking about stopping or on the way to maintenance.

2 Treatment approaches in Australia

Maintenance of change

The person has succeeded in stopping their harmful drug use and is concentrating on continuing that progress. An intervention technique known as relapse prevention teaches strategies for dealing with the pressures to relapse. Encourage patients to articulate the positive reasons for maintaining change to reinforce their decisions.

Changes in behaviour maintained for six months or more are usually associated with substantial improvements in the quality of life. Without such changes, the effort to change may not seem worthwhile and relapse becomes more likely. Quality of life includes factors such as employment, the quality of relationships, financial security, housing and spiritual support (variously defined). Drug and alcohol treatment services cannot be expected to address all these factors, but may be able to facilitate access to a range of advice and support services. These might include, but are not limited to housing services, financial support services, legal advice, employment, education and training.

Relapse

Relapse may occur for any number of reasons. It could be a reasoned choice about the benefits of returning to drug use or it could be a slip related to a variety of emotional or social triggers. Relapse may take the user into any of the other stages of behaviour.

The stages of change model highlights the relapsing-remitting nature of addiction. Relapse should not be seen as a treatment failure, but as a common characteristic of therapy. Most users will work through this cycle several times in their drug-using careers.

Craving

Craving is part of dependence on all substances. It is receiving increased recognition in the recently released Fifth Edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5), where it has been recognised as one of the fundamental criteria of substance use disorders, and as a feature that may persist during remission when other symptoms are quiescent. While sometimes presented as a simple phenomenon, craving is complex and multifaceted (Drummond, 2001; Tiffany, Carter, & Singleton, 2000). Craving is a psychological process separate from substance use. Craving can occur without substance use and substance use can occur without craving (Witkiewitz, Bowen, Douglas, & Hsu, 2013).

Animal models of craving can be divided into two domains: drug-seeking induced by drug or stimuli paired with drug-taking, and drug-seeking induced by an acute stressor or a residual negative emotional state, often a state of stress (Koob & Volkow, 2010). To some people craving means an urge to use drugs, to others it is a longing for something they miss, and still others desire the feeling they had when they were using drugs, without actually taking the drug.

2 Treatment approaches in Australia

Craving is a natural result of not having drugs after a long period of exposure. It is most intense when drug use is first stopped, especially when drugs are readily available. People usually don't crave drugs when they know for certain that drugs are not available. Craving is always temporary and often comes in waves (Drummond, 2001). Craving can be triggered externally by people, places frequented, and activities associated with drug use as well as drug-using equipment. Craving can also be triggered internally, by certain feelings, especially anger, stress, depression, anxiety and boredom. When things are going badly, people tend to long for the sense of tranquillity or the escape they experienced when they were using drugs. Craving may also be triggered by good events in people who have habitually used drugs as a form of celebration.

The role of treatment is to help patients identify the triggers for craving and to develop specific strategies to deal with and stop craving. However, patients should be encouraged not to dwell on craving as it increases the chance of relapse.

Strategies to remove triggers that might be cues for craving and drug use include:

- discarding all drug paraphernalia;
- breaking contact with dealers and drug-using friends;
- discarding any items that might be associated mentally with drug use; and
- using different travel routes to avoid passing places that might trigger craving.

Deal with craving with techniques that will disrupt the thinking process between the trigger and the craving. Keep busy – if your mind is occupied with something positive, it will not be occupied with craving and thinking about drug use.

Going for a walk, calling someone on the phone, exercising, taking a shower – these are all things that can help take your mind off craving. Use of other drugs, such as alcohol, may increase craving and lower drug resistance. Approaches to handle stress and depression without drug use are helpful, and maintaining motivation and self-efficacy are important. Talking to a partner, relatives and friends may help.

There are other specific strategies that can be used, such as thought stopping, or simply allowing your mind to ride along with the feeling until it is over. A proven technique for thought stopping is visualisation, which involves picturing a switch, or lever in your mind and then imagining yourself actually turning it off. Some people wear a loose-fitting rubber or elastic band on their wrist and snap the band and say "no". Other people have been able to exercise thought stopping with relaxation techniques and still others find it helpful to phone a friend, or to talk to someone with a similar life experience.

2 Treatment approaches in Australia

2.5.2 *Types of counselling*

Cognitive-behavioural approaches

Cognitive-behavioural therapy (CBT) examines the interplay between thoughts, behaviour and environment (Copeland, Gerber, & Swift, 2006).

The cognitive-behavioural approach to substance misuse incorporates many treatment interventions. This approach regards the etiology and persistence of problematic substance use as a maladaptive way of coping with problems, which can be changed through the application of combined cognitive and behavioural interventions. Interventions typically focus on enhancing patient motivation, providing new knowledge about substance use and its consequences, and challenging problematic beliefs about substance use and more general beliefs and cognitions.

Motivational Interviewing

Motivational interviewing (MI) is a method to work with ambivalence and help patients explore their reasons to change drug use. The basic elements of motivational interviewing include (K. Hall, Gibbie, & Lubman, 2012):

- express empathy
- develop discrepancy
- avoid argumentation
- roll with resistance
- support self-efficacy

The main aim of MI is to enhance the motivation of the patient to change (Copeland, et al., 2006).

Community reinforcement and contingency management

These are behavioural approaches directed at modifying behaviours that are underpinned by conditioned learning.

Contingency management rewards or punishes specific types of behaviours using a structured, transparent approach that increases learning of desired behaviours (WHO, 2009). Most programs focus on positive behaviours, with reinforcement for the desired behaviour. The elements of a contingency management program are:

- clear definitions of the desirable behaviour (e.g. abstinence from unsanctioned opioids);
- regular monitoring for the presence or absence of the desired behaviour (e.g. regular urine tests);
- specified rewards for the desired behaviour (e.g. money, vouchers, takeaway doses of substitution medication, or lottery tickets); and
- positive personal feedback from staff for the desired behaviour.

2 Treatment approaches in Australia

There is substantial research evidence supporting the effectiveness of contingency management, but relatively little uptake of the approach in practice (Hartzler, Lash, & Roll, 2012).

The Community Reinforcement Approach (CRA) is more broadly based in using social, recreational, familial and vocational reinforcers to aid patients in the recovery process (Abbott, 2009; Roozen et al., 2004). CRA integrates several treatment components, including building motivation to quit, helping cessation of drug use, analysing drug use patterns, increasing positive reinforcement, learning new coping behaviours, and involving significant others in the recovery process.

Elements of CRA[18] include motivational induction, monitoring pharmacotherapy, functional analysis, skills training, job finding, marital counselling, and social-recreational counselling. CRA has been effectively combined with contingency management as an adjunct to substitution treatment with methadone; CRA has also been integrated with unilateral family therapy into an approach called the Community Reinforcement Approach and Family Training (CRAFT).

Social Behaviour and Network Therapy (SBNT)

This approach was developed in the United Kingdom, originally for treatment of alcohol dependence (Copello, Orford, Hodgson, Tober, & Barrett, 2002), but more recently it has been adapted for drug users (Copello, Williamson, Orford, & Day, 2006). The basic principle of the approach is to encourage a change of social network, from one that is supportive of drug use to one that is supportive of abstinence.

Relapse prevention

Relapse prevention involves avoiding a return to problematic drug use and building a healthier self by becoming involved with activities that do not include drug use.

Relapse prevention would typically employ both CBT and MI techniques.

Psychological interventions incorporating relapse prevention aim to maintain long-term abstinence or moderate use and to decrease the severity of relapse if it does occur. The conceptual model of relapse prevention views relapse as a natural part of the process of change: lapses and relapses are viewed as opportunities for patients to understand their behaviour and develop new skills to deal with high-risk situations (Shand, Gates, Fawcett, & Mattick, 2003).

Counsellors can use relapse prevention training to give drug users the skills and confidence to avoid lapses to drug use, as well as the techniques to stop any lapses that do occur from becoming major relapses. A large part of this will be identifying high risk situations and learning to either avoid or to cope with them.

[18] See also http://pubs.niaaa.nih.gov/publications/arh23-2/116-121.pdf

2 Treatment approaches in Australia

The following strategies are useful in preventing and managing relapse:

- Enhance commitment to change (e.g. use motivational interviewing)
- Identify high-risk situations, for example:
  - When does the patient use heavily?
  - What situations have been associated with relapse in the past?
- Teach coping skills, for example: problem solving; social skills; self-management skills; self monitoring of drug use and drug-related harm
- Develop strategies that can be part of a relapse drill
  - What should the patient do in the event of a lapse occurring?
  - Where can they get support?
  - What role can friends/family provide?
- How soon should the patient make an appointment to come back to your practice?

Relapse means returning to the behavioural patterns of addiction. These behaviours often return before the actual drug use begins again. Learning to recognise a relapse when it is just beginning can help stop the process before drug use begins again.

As drug use increases, it becomes increasingly more difficult to keep life under control. The loss of control may result in desperate actions to maintain normal appearances. These desperate actions define addictive behaviour and include lying; stealing; lack of responsibility (at work and home); lack of reliability (late for appointments, breaking promises); carelessness with health and hygiene; impulsiveness; obsession and/or compulsion; poor work habits; loss of interest in family life, recreation and hobbies; isolation; using other drugs, alcohol or prescribed medication; stopping prescribed medication; loss of self-control; and loss of ability to cope with everyday problems.

Becoming aware of addictive behaviours and learning to recognise them when they begin helps to identify when additional effort is needed to prevent relapse.

Triggers for relapse can be both external and internal. Avoidance of certain negative emotional states is important to prevent relapse. A well-established acronym for the most common negative feelings that trigger return to drug use is HALTS, which stands for:

- Hunger – for comfort and attention as well as food;
- Anger – the intense irritability experienced in the early stages of recovery can result in intense anger or rage. These feelings cause the loss of perspective and rationality and may trigger relapse.
- Loneliness – it is very hard to give up friends and activities that are associated with a drug-using lifestyle and non-using friends and family members often resist contact with a person who is addicted.
- Tiredness – sleep problems occur frequently during recovery. Being tired often triggers relapse but the feelings of increased vulnerability and exhaustion are temporary.
- Sick or Stressed –recovery can feel like a negative state, something to be endured, which increases vulnerability to relapse.

2 Treatment approaches in Australia

To be successful in recovery addicts must learn to identify and face their true feelings. Emotions are often manifested outwardly, through physical symptoms (stomach ache, headache, nail-biting, shouting). It is important to recognise these outward signs of emotion so they do not continue to build inside. Other times physical symptoms may be the cause of feelings, such as depression or protracted abstinence syndrome. It is also important to recognise when these occur so action can be taken.

Counselling encourages people to look at their feelings, how they affect them and others around them. Recovery entails learning when and how to express feelings. Changing behaviour and doing something different is another way of coping with feelings.

Prominent theories and research highlight the importance of social processes and social network characteristics as potent correlates of alcohol use and the relapse-recovery process. From a treatment perspective, assessing what patients do and with whom, are critical variables to consider in relapse prevention planning. Treatment programs typically work with patients to help them identify and cope with high risk individuals, settings and activities that may undermine recovery efforts (J. F. Kelly, Magill, & Stout, 2009).

2.5.3 Setting for counselling

Psychological interventions may be offered on a one on one or group basis. It is important to offer a range of treatment services to patients and some may prefer to participate in a group model for psychological interventions. Whilst group work may not be the best fit for all patients, for some it may present an opportunity to reduce isolation. Choice is an important determinant of the perceived value of group counselling for service users.

Drug users who participated in interviews about treatment experience, had largely not tried group therapy, and while not opposed in principle were often not attracted to the idea (Holt, et al., 2007). The need to talk in front of other people (particularly about illicit drug use) was a commonly cited barrier to participating in group work. Some users found that it was an important first step in addressing problems underlying their drug dependency and that group participation lessened their sense of isolation. Choice was an important determinant of the perceived value of group counselling for service users. Little value was generally placed on group participation by those who had participation imposed on or required of them (such as by a court).

2.5.4 Psychosocial support

Psychosocial assistance in the treatment of opioid dependence refers to the many ways in which professional and non-professional members of society can support the psychological health and the social environment of the opioid user, to help improve both the quality and duration of life (WHO, 2009). Assistance can range from the simple (e.g. provision of food and shelter) to the complex (e.g. structured psychotherapy).

2 Treatment approaches in Australia

It is one of the key roles of treating clinicians to assist in this process, either as direct service providers, or as case managers referring the patient on to appropriate services for other areas of their lives. Providing reinforcement and referral to vocational, financial, housing and family assistance contributes positively to the progress of treatment.

Studies of self-recovery by drug users have shown that access to formal welfare supports, together with encouragement from friends, partners, children, parents and other significant individuals, is commonly involved in the pathway out of addiction (Groh, Jason, & Keys, 2008).

Self-help groups

Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) are the best known of the self-help or mutual-help groups; they are free, voluntarily-attended gatherings characterised by working together on a common problem, self-directed leadership, and the sharing of experiences (Groh, et al., 2008).

AA and NA espouse a disease concept of drug and alcohol dependence with the potential for recovery, but not cure, for those who adhere to it. The concept of NA and AA is that by working through the 12 steps, addicts will experience personal growth, and be “in recovery”, an ongoing lifelong process of increasing insight and commitment to change (Cook, 1988).

Findings cited (Kaskutas, 2009) in support of the effectiveness of AA include:

- rates of abstinence are approximately twice as high among those who attend AA;
- higher levels of attendance are related to higher rates of abstinence;
- these relationships are found for different samples and follow-up periods;
- prior AA attendance is predictive of subsequent abstinence; and
- mechanisms of action predicted by theories of behaviour change are evident at AA meetings and throughout the AA steps and fellowship.

Among those who start NA and AA attendance, the majority (85% and 91%, respectively) stop NA and AA attendance for a month or longer. While data suggest that many people subsequently recommence NA or AA attendance, in general NA or AA attendance and involvement decrease over time (Krentzman et al., 2011). The emphasis on spirituality and addiction as a disease by NA have been found not to be significant reasons for non-attendance at NA – attitudes towards drug use are more powerful predictors of non-attendance (Christo & Franey, 1995).

One study of drug users attending NA in London, UK, found that after six months, 46% were abstinent, and 50% were still attending NA. Among attenders, the mean attendance was 2.2 meetings per week (Christo & Franey, 1995).

Aspects of AA or NA that have been suggested as helping to promote behaviour change include spirituality, self-efficacy, coping and social support (Groh, et al., 2008). The 12-step experience creates a sense of communality, and this solidarity is an important aspect of the program’s spiritual nature (Galanter, 2006). Several longitudinal studies indicate that AA involvement helps promote increased social resources and higher quality relationships involving friends. Studies indicate that greater AA involvement is related to positive functional types of support such as higher friendship quality and more friend resources (Groh, et al., 2008).

2 Treatment approaches in Australia

Studies indicate that both the receipt and provision of help within AA can aid in recovery. Providing help to others may be just as useful in maintaining abstinence as the receipt of help. Learning how to assist others may be a major benefit of the 12-step program (Groh, et al., 2008). Attending self-help groups in itself is not sufficient – it is participation in self-help group meetings that is critical (Weiss et al., 1996).

There is growing interest in alternative approaches to self-help or mutual support, such as SMART (Self-Management and Recovery Training) Recovery. This is a cognitive approach that promotes, but does not require abstinence, through the provision of a set of tools and skills to support recovery. Such approaches are particularly useful for patients of substitution treatment programs who might benefit from mutual support and networking with other recovering drug users but who can be excluded by the drug-free emphasis of AA and NA.

LINK

See www.smartrecovery.org

See www.smartrecoveryaustralia.com.au

Drug users who participated in interviews about their treatment experiences and who had experienced peer involvement and peer work were extremely positive about its effects on other service users, the wider drug using community and peer workers themselves. Peers employed in treatment services or in voluntary programs noted the value of being able to contribute in an inclusive and non-judgemental environment. One participant specifically identified undertaking peer work as a form of treatment in itself (Holt, et al., 2007).

Aftercare

It is recognised that the period immediately following treatment represents a time of high risk for relapse, and as such appropriate support is important at this time. Some structured treatment programs distinguish a period of less intensive treatment after a patient has completed the main program, called aftercare. It is based on the intention to provide ongoing support to patients at the level required to maintain the earlier benefits and goals. Due to the high potential for relapse following discontinuation of treatment, relapse prevention is a strong feature of aftercare. The provision of aftercare offers the opportunity to reinforce treatment interventions and may reduce the number, length and severity of relapse (National Treatment Agency for Substance Misuse, 2006).

Regular phone contact, scheduled appointments and unscheduled or drop-in visits may all be available in aftercare programs. Patients may also be encouraged to access self-help groups and other general support and advice services as required. Clearly, a supportive family and community environment will also be conducive to helping in the recovery of people who have received treatment for problematic drug use (UNODC, 2003).

2 Treatment approaches in Australia

2.6 Issues that may impact on treatment

A number of population groups and circumstances can be identified where additional needs potentially exist. These groups may have higher rates of substance use than the general population, substance use may be complicated by other health issues, or mainstream alcohol and other drug treatment services may need to be adapted to suit the particular cultural and other characteristics of the population group. Linkages between alcohol and other drug treatment services, other health and social service agencies in the government and non-government sectors are particularly important to meet the needs of patients in these population groups. In some instances such linkages may involve the provision of advice or assistance relating to patients being cared for within other health sectors who also have alcohol and other drug use problems; in other instances linkage may involve connecting patients of alcohol and other drug treatment services with agencies that can meet their additional needs.

People with problematic alcohol and other drug use typically need to deal with a range of health and social issues for full rehabilitation to be achieved. The social and medical issues commonly associated with problematic alcohol and drug use may precede problematic use or may develop as a consequence of this use.

Co-existing issues include homelessness, intellectual disability and acquired brain injury, mental health problems and medical problems. Life issues (health conditions such as hepatitis C, poor housing conditions, restricted income and debt, having a criminal record, family issues and relationship problems) form a complex web of problems that adversely affect the ability to engage and remain in treatment (Holt, et al., 2007).

2.6.1 Aboriginal and Torres Strait Island People

In recognition of the challenges faced by Aboriginal and Torres Strait Islander peoples, this group warrants special consideration. The aim is to provide a diversity of treatment options to reflect the diversity of the Aboriginal and Torres Strait Islander peoples, maximise health, wellbeing and social functioning, as well as to reduce the risks to community safety and health with a culturally sensitive approach. This is especially important given the substantially higher rates of mortality and morbidity experienced by this population group.

Existing mainstream models of practice in the drugs and alcohol field have been developed primarily within western systems of knowledge and may ignore an Aboriginal ‘worldview’. Application of these models to working with Aboriginal people can be detrimental, to the extent that some approaches can directly undermine Aboriginal cultural ways of working resulting in Aboriginal people feeling disempowered as their cultural beliefs/values and family systems are ignored, misunderstood or disrespected. This can result in Aboriginal people disengaging from seeking support and treatment. In the past there have also been efforts to impose approaches from Indigenous people in other countries on Aboriginal Australians. This can also have devastating outcomes as it weakens Australian Aboriginal culture and often these approaches are embedded in western disease ideology which is very different to an Aboriginal concept of holistic health and well-being.

2 Treatment approaches in Australia

Models of drug and alcohol treatment, framed from within an Aboriginal cultural context and developed by Aboriginal people, are likely to be more effective. Such models respect the legitimate rights, values and expectations of Aboriginal people and acknowledge the diversity within and between Aboriginal communities living in remote, regional and metropolitan areas. These models:

- incorporate an Aboriginal holistic concept of health and wellbeing;
- are grounded in an Aboriginal understanding of the historical factors, including traditional life, the impact of colonisation and the ongoing effects;
- aim to strengthen Aboriginal family systems of care, control and responsibility;
- address culturally secure approaches to harm reduction; and
- work from within empowerment principles.[19]

For resources on health issues for Aboriginal and Torres Strait Islander people, see www.healthinfonet.ecu.edu.au.

2.6.2 Women

Women are more vulnerable to the adverse medical and social consequences of substance use and dependence. For substance use disorders, including alcohol, opioid and cannabis dependence, females advance more rapidly from use to regular use to first treatment episode than do their male counterparts. In addition, when they enter treatment, in spite of fewer years of use and smaller quantities of substances used, the severity of their symptoms is generally equivalent to that of males. Even with fewer years of substance use, at treatment entry, females average more medical, psychiatric, and adverse social consequences of their substance use disorders than males (Greenfield et al., 2007).

Compared with men, women who misuse alcohol and other drugs tend to have elevated histories of childhood trauma and abuse, interpersonal violence in adolescent and adult relationships, criminal activity, involvement with child protective services, homelessness, and dependence on others for financial support (Prendergast, Messina, Hall, & Warda, 2011).

Studies in the USA and Australia have consistently found relatively low proportions of women in drug and alcohol treatment programs compared with the prevalence of these disorders among women in the general population. Specific barriers to treatment entry that may be faced by women include (Greenfield, et al., 2007):

- issues relating to pregnancy and childcare, including lack of services, fear of losing custody of children and fear of prosecution;
- economic barriers arising from lower educational attainment and less frequent employment;

[19] Marsh, Ali; Dale, Ali and Willis, Laura (2007). *Evidence Based Practice Indicators for Alcohol and Other Drug Interventions: Literature Review*. Published by Drug and Alcohol Office, Western Australia. Available from http://www.dao.health.wa.gov.au. Accessed 15/4/2013.

2 Treatment approaches in Australia

- higher rates in women of co-occurring psychiatric disorders, such as mood, eating, anxiety and post-traumatic stress disorders that may make it difficult to obtain appropriate treatment for both disorders;
- trauma histories, including sexual and physical assault and abuse, may make certain treatment approaches or mixed-gender treatment programs less desirable for women;
- lack of family or partner support to enter treatment;
- greater social stigma and discrimination.

Men and women can be treated in the same facility, providing that culturally appropriate and gender-specific needs can be taken care of.

It has been argued that there is a need for gender-responsive (meaning programs designed to provide a secure environment for women to safely discuss histories of trauma, abuse, and addiction without fear of judgement, and which are implemented in a manner that promotes psychological growth and prosocial behaviours among women) and gender-specific (i.e. women only, but not necessarily gender-responsive) treatment programs because the treatment issues and needs of women are quite different to those of men, reflecting broader societal gender differences, including women's lower economic status and primary responsibility for child-rearing (Prendergast, et al., 2011).

Programs specifically for women tend to use a more supportive and less confrontational approach to treatment. Some women-only programs provide classes on self-esteem, assertiveness training, healthy versus disordered relationships, physical/sexual abuse, trauma, parenting, and sex- and health-related issues. Women-only programs are also more likely to provide assistance with housing, transportation, job training, practical skills training, and on-site child-care services. These are known as wraparound services and research suggests that the provision of such services can greatly improve the likelihood of successful recovery for women (Prendergast, et al., 2011).

Women are often less likely to enter and remain in mixed gender treatment programs compared with men. Gender-specific factors that have been associated with retention of women in treatment include a higher prevalence of depression, involvement with drug-dependent partners, histories of sexual or physical abuse, prior arrests for sex work, sexual harassment from both male participants and counsellors, and childcare responsibilities (Prendergast, et al., 2011).

Although women-only treatment has not been consistently shown to be more effective than mixed-gender treatment, some evidence indicates that women are less likely to drop out of women-only programs, which is likely to lead to better outcomes. Moreover, greater effectiveness has been demonstrated by treatment programs that address problems and issues common among substance-abusing women, such as childcare issues, services for pregnant and postpartum women, or histories of trauma and/or domestic violence (Prendergast, et al., 2011).

While there is evidence that specialised women's programs are successful at attracting women who would otherwise not seek treatment, randomised health services studies with sufficient numbers of minority women (and women with children) are needed to determine whether women's programs are especially effective for special populations. Findings of a study by Kaskutas et al. (2005) suggest that high-quality mixed-gender and women's day treatment programs can serve women equally well.

2 Treatment approaches in Australia

2.6.3 *Pregnancy and breastfeeding*

Pregnant opioid users not in treatment

Substance use during pregnancy has an adverse effect on maternal wellbeing, foetal development, perinatal outcomes and long term individual development, including increased risk of development of substance use disorders (Bauer et al., 2002; McDonald, Vermeulen, & Ray, 2007). Pregnancy is often a time of high motivation for women with substance use issues and presents an opportunity for women to reduce their substance use and engage in treatment. However, some women may be reluctant to present for help with substance use during pregnancy due to stigma and concern regarding the involvement of child protection services.

Substance use should be routinely asked about in all women presenting for antenatal care. This should generally occur at the first visit and periodically throughout the pregnancy. Information regarding prescribed, non-prescribed, licit and unsanctioned drug use including quantity and frequency should be recorded. Use of a validated screening instrument such as the Alcohol Use Disorders Test or WHO Alcohol, Smoking, Substance Involvement Screening Test (ASSIST) may be used and may increase detection of substance use.

LINK

For information on the ASSIST see http://www.who.int/substance_abuse/activities/assist/en/

Women with substance use disorders during pregnancy should be referred to specialist, multidisciplinary drug and alcohol antenatal clinics, where they exist. Women with substance use problems require a multidisciplinary approach to management to ensure continuity of care and appropriate services are in place through to the postnatal period and thus minimise post-birth consequences for both them and their baby. Such a multidisciplinary team typically would include midwives, obstetricians, paediatricians, perinatal psychiatrists, social workers, child protection workers and addiction specialists.

Patients seeking to remain opioid-free during pregnancy should have additional monitoring and support, as pregnancy can be a time of considerable psychological stress. While pregnancy is often a time when women become motivated to stop drug use, motivation alone may not be sufficient to ensure sustained remission from all substance use.

Pregnant women who are dependent on opioids are at high risk of experiencing complications, generally as a result of:

- inadequate antenatal care;
- poor housing, poor nutrition and violence from partners;
- repeated cycles of intoxication and withdrawal which can harm the fetus or precipitate premature labour or miscarriage;
- use of a range of substances (including tobacco, cannabis, alcohol, benzodiazepines and amphetamines);
- mental health problems (e.g. anxiety,depression, PTSD).

2 Treatment approaches in Australia

Substitution treatment is the preferred approach for the opioid dependent pregnant woman (Binder & Vavrinková, 2008; Burns, Mattick, Lim, & Wallace, 2007; Fajemirokun-Odudeyi et al., 2006; Einat Peles, Schreiber, Bloch, Dollberg, & Adelson, 2012) due to its capacity to:

- improve access to antenatal care with improved birth outcomes;
- reduce heroin and other drug use, and improve the health of pregnant women;
- reduce maternal and infant deaths associated with heroin use;
- reduce the spread of blood-borne communicable diseases associated with injecting drug use; and
- facilitate the improvement in social functioning of the mother.

Pregnancy and opioid substitution treatment

Pregnant women in opioid substitution treatment should be encouraged to continue in treatment for the duration of their pregnancy and for a substantial period after birth while they are caring for an infant. Although many women want to cease using opioids when they find out they are pregnant, opioid withdrawal is a high-risk option because a relapse to opioid use will expose both mother and child to the risks of unsanctioned drug use and affect the mother's capacity to care for the child. Opioid substitution treatment has better outcomes, both in access to antenatal care and ongoing stability, than withdrawal during pregnancy (H.E. Jones, O'Grady, Malfi, & Tuten, 2008; Einat Peles, et al., 2012).

Although there is no strong evidence, it is widely accepted that withdrawal is not advisable prior to 14 weeks, or after the 32nd week of pregnancy (K. Kaltenbach, Berghella, & Finnegan, 1998; A. R. Lingford-Hughes, et al., 2012), due to the risk of inducing spontaneous abortion or premature labour. Relapse to opioid use during pregnancy can also result in poor obstetric outcomes. Opioid substitution treatment is thought to have minimal long-term developmental impacts on children when compared to the risk of uncontrolled opioid use during pregnancy and resulting harms (WHO, 2009).

Methadone and buprenorphine can both be considered first line options for the management of opioid dependence during pregnancy. Both medications are safe and effective during pregnancy for both mother and neonate (Dunlop et al., 2009; Gaalema et al., 2012; Hendrée E. Jones et al., 2012; H.E. Jones, Kaltenbach, Heil, & Stine, 2010). Indeed, buprenorphine may be associated with more favourable neonatal growth and behavioural parameters than methadone (Coyle et al., 2012; Kakko, Heilig, & Sarman, 2008; Welle-Strand et al., 2013). Opioid substitution treatment of opioid dependent women with either methadone or buprenorphine is associated with improved fetal development and infant birth weight, and a reduced risk of perinatal and infant mortality. There is substantial experience in the use of methadone in pregnancy over more than four decades. The benefits of methadone have been demonstrated in observational studies and supported in reviews and meta-analyses (Dunlop, et al., 2009). A multi-site RCT of methadone and buprenorphine in pregnancy demonstrated that while a higher proportion of women discontinued buprenorphine compared to methadone (33% vs 18%, respectively), the proportion of women with infants with neonatal abstinence required pharmacological treatment was similar in the two groups (57% methadone, 47% buprenorphine). However, the profile of the neonatal withdrawal syndrome was less severe in the buprenorphine-exposed infants, with these infants requiring less morphine and shorter hospital stays than those exposed to methadone (10 days vs 17.5 days, respectively).

2 Treatment approaches in Australia

Given the positive results regarding the use of buprenophine in pregnancy across multiple studies, involving nearly 900 buprenorphine-exposed infants (Hendrée E. Jones, et al., 2012), opioid substitution treatment with buprenorphine should be considered a first-line treatment for opioid dependence in pregnancy, alongside methadone maintenance. As there is now a substantial literature comparing buprenorphine to methadone in pregnancy, the likelihood of a severe adverse event not already reported in the literature is small.

Use of benzodiazepines or other drugs as well as methadone or buprenorphine is associated with longer-lasting neonatal abstinence syndrome (Welle-Strand, et al., 2013) and longer duration of stay in hospital (Wachman et al., 2011). Polydrug exposure may potentiate the effects of methadone on the fetus and infant (L.M. Jansson et al., 2012).

Naltrexone treatment and pregnancy

The safety of naltrexone in pregnancy is not established.

Patients on naltrexone treatment should be advised that they may experience increased sex drive and fertility compared to when they were taking opioids and to use reliable contraception to avoid pregnancy. Female patients in particular should be counselled about avoiding pregnancy while taking naltrexone as its safe use in pregnancy and while breastfeeding has not been established. The decision to continue naltrexone treatment in pregnancy involves careful assessment of the relative risks to the fetus and the likelihood of relapse to heroin use.

LINK

A7.1 Pregnancy and breastfeeding

Managing pregnancy

Regular examination of the patient during pregnancy is important in order to:

- assess individual response to adequacy of dose of medication and alter as required;
- discuss the effect of methadone or buprenorphine in pregnancy;
- determine and advise on any other drug use;
- discuss likely withdrawal effects on the baby after delivery and how this will be managed;
- discuss any other issues that may arise, including implications of hepatitis C, hepatitis B or HIV seropositivity where appropriate.

Pregnant women should be maintained on an adequate dose of methadone or buprenorphine to achieve stability and prevent relapse or continued unsanctioned opioid drug use. Target doses for both medications are the same as for patients who are not pregnant.

In the second and third trimester, methadone doses may need to be increased, due to increased metabolism and circulating blood volume. Splitting the dose into two 12-hour doses may produce more adequate opioid replacement in this period (A. R. Lingford-Hughes, et al., 2012). After birth, the dose of methadone may need to be adjusted again as some of these changes reverse (WHO, 2009). Buprenorphine dose increments may be clinically indicated during pregnancy, but splitting the dose is not usually necessary. There is little evidence that limiting the dose of opioid agonist reduces the risk of neonatal abstinence syndrome. Pregnant women should be counselled to prioritise maintaining stability and avoiding risk of uncontrolled opioid use.

2 Treatment approaches in Australia

Dose reductions or detoxification during pregnancy

For some women pregnancy is a significant motivating factor to attempt abstinence. However, opioid withdrawal in the first trimester of pregnancy is thought to be associated with an increased risk of miscarriage, and opioid withdrawal in the third trimester of pregnancy may be associated with fetal distress and death (K. Kaltenbach, et al., 1998; A. R. Lingford-Hughes, et al., 2012). Therefore, it is important that pregnant women are not exposed to withdrawal during the first and third trimesters.

Neonatal monitoring

All babies born to opioid dependent mothers should be observed by experienced staff for the development of withdrawal signs or any other adverse events. This group of children should be followed up by paediatricians with experience in caring for children exposed in utero to drugs of dependence. Long-term follow-up (e.g. 12 to 24 months) may be required to monitor for developmental abnormalities.

Withdrawal symptoms usually start within 48 hours of delivery but may be delayed for 7-14 days in a small number of cases. Monitoring should continue for at least seven days in most situations. It is recommended that a validated scale, such as the Modified Finnegan Scale (see Appendix 2) be used to assess the presence and severity of the neonatal withdrawal syndrome. Although complex, this is the most comprehensive scale available and the most widely referenced (Lauren M. Jansson, Velez, & Harrow, 2009).

LINK

Appendix 2: Assessment of opioid withdrawal.

The occurrence and severity of neonatal withdrawal is likely to be influenced by multiple factors that make it difficult to predict (Karol Kaltenbach et al., 2012). However, severity appears to be largely unrelated to the dose of opioid medication (Bakstad, Sarfi, Welle-Strand, & Ravndal, 2009; Berghella et al., 2003; B.J. Cleary et al., 2010; Brian J. Cleary et al., 2013; Seligman et al., 2010). Severity of withdrawal is probably ameliorated if neonates can be kept with their mothers rather than in the neonatal intensive care nursery (Abrahams et al., 2007), which may be stressful and overstimulating.

Supportive treatment involves minimising environmental stimuli and enhancing the baby's comfort and may include:

- soothing by holding close to the body or cuddling;
- keeping nostrils and mouth clear of secretions;
- use of a dummy to relieve increased sucking urge;
- frequent small feeds.

Indications for treatment:

- Seizure
- Weight loss (poor feeding, diarrhoea and vomiting, dehydration)
- Poor sleep
- Fever

Treatment should be based on the severity of the withdrawal signs. Treatment should be commenced when a score of 9 or more on the Finnegan Scale (see Appendix 2) is recorded on two consecutive observations. Improvement should be monitored using scores on the Finnegan Scale.

2 Treatment approaches in Australia

A systematic (Cochrane) review found that opiates compared to supportive care may reduce the time to regain birthweight and duration of supportive care but increase the duration of hospital stay. When compared to phenobarbitone, opiates may reduce the incidence of seizures but there is no evidence of effect on treatment failure. Compared to diazepam, opiates reduce the incidence of treatment failure. The authors suggest restricting opiate treatment to infants of mothers who used opiates only. However, they noted methodological limitations reduce the strength of this recommendation (Osborn, Jeffery, & Cole, 2010a).

A second systematic (Cochrane) review by the same authors concluded that infants with neonatal abstinence syndrome due to opiate withdrawal should receive initial treatment with an opiate. Where a sedative is used, phenobarbitone should be used in preference to diazepam. In infants treated with an opiate, the addition of phenobarbitone or clonidine may reduce withdrawal severity (Osborn, Jeffery, & Cole, 2010b).

However, given that treatment with opioids may depress respiration, extreme caution should be used.

It is recommended that neonatal care be managed in collaboration with a specialist obstetric or paediatric service experienced in the management of babies born to drug dependent mothers.

Breastfeeding

Although methadone and buprenorphine are detectable in breast milk, the levels are low and are not thought to significantly affect the infant (Lauren M. Jansson, et al., 2008). Given that the infant swallows the milk, absorption of buprenorphine from breast milk would be expected to be minimal. However, there is a lack of robust research evidence regarding the safety and effects on development of breast fed babies exposed to buprenorphine. In the absence of adequate information of the effects of buprenorphine on breastfeeding infants, breastfeeding should be approached with some caution. Consultation with a specialist paediatric unit with substance use expertise is advised.

Breastfeeding, on the other hand, has many benefits, including mother-infant bonding, nutrition and prevention of childhood illness, and may reduce the severity of the neonatal withdrawal syndrome as well as providing substantial financial advantages for mothers on low incomes. Opioid-dependent mothers should be encouraged to breastfeed (WHO, 2009), with the possible exception of women who continue to use substances, especially where there is a risk of over-sedation and smothering of an infant (e.g. benzodiazepines, alcohol).

2 Treatment approaches in Australia

2.6.4 *Parenting and child protection issues*

Parental substance use can be both an indicator and a compounding factor of limited parenting capacity. While substance use alone does not predict child maltreatment (Doris, Meguid, Thomas, Blatt, & Eckenrode, 2006; Jaudes, Ekwo, & Van, 1995; Kroll, 2004; Smith, Johnson, Pears, Fisher, & DeGarmo, 2007; Street, Harrington, Chiang, Cairns, & Ellis, 2004; Velez et al., 2004) it is the single most common factor predicting removal of children from parental care (Banyard et al 2003; Kelley 1992; Smith & Testa 2002; Suchman et al 2006), and in investigated child fatalities[20] Gibson & Vulliamy, 2010; Palmiere, Staub, La, & Mangin, 2010).

The multitude of parental risk factors (including comorbid mental health problems, partner violence, history of childhood trauma, single/unsupported parenting, homelessness, social isolation and poverty) combined with ongoing substance use can impair parenting and significantly impede child developmental health and wellbeing and attachment security. Parents who use substances may also have a significantly impaired ability to understand and respond to their infant's basic developmental needs (Cleaver, Unell, & Aldgate, 2011; Mayes & Bornstein, 1996) which can place children as significant risk of neglect or other harm.

Particularly during the years before school age, drug and alcohol services may be the only agency with which this patient group maintains regular contact. Therefore, it is vital that clinicians ask all individuals presenting to their service if they have any children in their care or if they assume a caregiving role for other children (e.g. their partner's children). It is also important to ask the age of the children to better identify the impact of risks to the infant or child(ren). Clinicians should ascertain as much information as possible about development of any children (immunisation, nursing checks, school etc) as well as any difficulties the parent may have in providing for physical and psychological needs of children. This will assist in making informed decisions about mandatory reporting or making appropriate referrals to support services (such as intensive parenting support, parent and infant mental health, child and family health, etc).

[20] NSW Government. *Child deaths 2010 annual report. Learning to improve services.* Available from http://www.facs.nsw.gov.au/__data/assets/pdf_file/0013/251320/Child_Deaths_2010_Annual_Report_final_online_version_141211.pdf. Accessed 29/5/2013.

2 Treatment approaches in Australia

2.6.5 Adolescents

Young people experiencing substance misuse problems may require specialised support and assistance to overcome their problems and navigate their way to a full and productive adulthood.

It is recognised that attracting and retaining young people in treatment for substance problems is challenging for a number of reasons (National Treatment Agency for Substance Misuse, 2006). An examination of treatment services for young people in the UK recommended that in order to be 'youth friendly', services should aim to:

- make their services interesting and responsive to young people's needs;
- gain the confidence of young people by being respectful, trustworthy and e motionally warm;
- show that they care about the young person, are committed to helping them and flexible in helping to meet the young person's needs; and
- provide practical support and semi-formal contact.

The complex interacting factors that may impact on alcohol and drug treatment provision for young people indicate the need for specialised youth service providers. Young people face a range of needs, not all of which are drug-related and therefore specialist youth services are best able to manage a young person's substance misuse problems, and also provide integrated care services to address multiple needs or have the capacity to actively link patients to other services as required.

Issues such as whether parental consent is required to receive services and what types of treatment are considered appropriate for young people need to be considered in service design and delivery.

For the most part, young people experiencing drug and alcohol problems do not require intensive medical support through inpatient services. Young people are more effectively managed in a community setting. Treatment of young people early in the course of drug use presents the opportunity to prevent comorbidities associated with drug use, including acute and chronic medical condition as well as psychiatric and social complications (Levy, Vaughan, Angulo, & Knight, 2007).

Younger patients who present for treatment of drug dependence often have a shorter history of drug use than treatment-seeking adults (Levy, et al., 2007). It is preferable that treatment services for minors are provided separately from services for adult users to avoid exposing them to adults who may have more entrenched drug use and anti-social behaviours.

In treating adolescents, the emphasis should be on psychosocial responses, harm reduction and family intervention approaches.

The family experience is an important factor in the development and treatment of alcohol and other drug use by young people and addressing family issues and family involvement are important components of treatment. Factors about the quality and consistency of family management, family communication, family relationships and parental role-modelling have been consistently identified as predictors of drug use (Spooner, 1999).

2 Treatment approaches in Australia

If family issues are a contributing factor to the adolescent's drug problem, adolescents who return to the same home environment are likely to relapse. Conversely, the family can be a protective factor and can support the treatment program and the adolescent in achieving treatment goals.

Family involvement can be difficult to achieve and is even less likely if it is not actively sought. In cases where family involvement is not possible, it is still important to deal with family issues with adolescent patients. In some cases separation from, rather than involvement with, the family could be indicated (Spooner, 1999).

Whilst there is some support for the efficacy of residential treatment for young people, it is an expensive and potentially invasive option. Long-term residential places or beds for the rehabilitation of young people with drug use issues is complex as some may also be homeless, have mental health issues, or be unwilling to enter mainstream residential services. As such, it should only be considered where external supports (family, school/ work, accommodation, income etc) have broken down, are openly hostile, are non-existent, or where there are significant mental health and other behavioural concerns present. Other risks associated with residential treatment include removing the young person from the functional aspects of their lives and exposing them to drug using peers (Stubbs, Hides, Howard, & Arcuri, 2004).

For young people, outpatient drug-free treatment is associated with lower rates of retention in treatment and limited impact on opioid use relative to substitution treatment (Kornor, Waal, & Ali, 2006). Hence substitution treatment should be available for young opioid users who are not attracted into or do not respond to psychosocial treatment alone but should be used only after careful assessment of the risks and benefits and in the context of a comprehensive treatment plan. Buprenorphine is preferred over methadone for substitution in young people because of its lesser opioid effects, easier withdrawal and lower risk of overdose. This is supported by reports of adolescent patients who have benefited from substitution treatment with buprenorphine (Levy, et al., 2007; Moore, Marsch, Badger, Solhkah, & Hofstein, 2011; Smyth, Fagan, & Kernan, 2012; Woody et al., 2008) Those who do not respond to buprenorphine can readily be transferred to methadone.

While buprenorphine offers the possibility of easier, earlier cessation of treatment compared to methadone, one randomised controlled trial (Woody, et al., 2008) has shown better outcomes with extended rather than short-term buprenorphine treatment in an adolescent population. This emphasises the need, as with adults, for treatment to be suited to the individual.

2.6.6 Comorbid mental health conditions

Dual diagnosis, or psychiatric comorbidity, refers to the coexistence of any psychiatric disorders and substance use disorders in the same individual. In practice the term is often more specifically restricted to include severe mental illness (psychosis, schizophrenia, bipolar affective illness) and substance misuse disorder. However, mood and anxiety disorders are common and may be significant factors in the initiation and maintenance of substance use.

2 Treatment approaches in Australia

There are now a large number of studies that have investigated rates of alcohol and other drug use amongst people with mental illness. While the detail of the estimates vary according to the population groups studied, a consistent finding is that the misuse of alcohol and other drugs is more common among people with mental illness compared with the general population (Flynn & Brown, 2008).

Studies have also consistently found that mental health disorders are more common in people who use alcohol and other drugs, with some variability between studies depending on the population group and study methodology. Associations are generally greater for those meeting criteria for dependence, and greater for mood rather than anxiety disorders (Conway, Compton, Stinson, & Grant, 2006).

A very high rate of mental health conditions accompanies opioid dependence These include depression, social phobia and other anxiety disorders (A. R. Lingford-Hughes, et al., 2012). Many opioid users (especially female) exhibit symptoms of anxiety and depression at the time of presentation for treatment (Gordon, 2008). Depression may contribute to, be caused by, be independent of, or exacerbate problems of opioid dependence. Sometimes depression resolves with treatment of the opioid dependence (Gordon, 2008). However, in some patients there are persistent deviations in mood and temperament, which warrant a further diagnosis.

Most, but not all, studies link psychiatric distress to poorer treatment outcome. Depression has been found to predict poor psychosocial functioning and to increase the risk of relapse to opioid use in the event of life crises.

Mentally ill patients who are substance misusers (compared to non-users) have higher readmission rates and increased use of inpatient services. Substance use and dependence in the context of severe psychiatric disorder results in poorer social functioning, greater psychiatric service utilisation and overall poorer prognosis (Bellack & Gearon, 1998; C. H. Brown, Bennett, Li, & Bellack, 2011; DiClemente, Nidecker, & Bellack, 2008).

Treating clinicians need to be skilled in the assessment, management and appropriate referral of people with comorbid mental health problems (Gordon, 2008) (Baker, Gowing, Lee, & Proudfoot, 2004).

The risk of people with comorbid conditions “falling through the gap” between mental health and drug and alcohol services is an ongoing concern. The establishment and maintenance of collaborative networks and referral pathways are important to ensuring the provision of adequate and appropriate care for comorbidity.

Patients with more severe substance use disorders and less severe mental disorders would be best treated in specialist drug and alcohol facilities, with service integration and linkages with the mental health sector. Conversely, those patients with a more severe mental disorder and a less severe substance use disorder would be best treated in a mental health service with linkages to drug and alcohol treatment services. It would be ideal if patients with lower severity mental disorder and lower severity substance use could be treated outside the specialist treatment systems, however this would require an integrated holistic service approach to ensure the range of needs are met. Patients with more severe mental disorder and more severe substance use disorders need the most intensive integrated treatment from both specialist mental health and specialist drug and alcohol treatment services.

2 Treatment approaches in Australia

Accurate assessment of patients with psychiatric symptoms and substance misuse is difficult. The main reason for diagnosing comborbidity and the relationship between comorbid conditions, is to select appropriate treatment (Harrison & Abou Saleh, 2002; Williams, 2002).In some cases it is not possible to determine which disorder is primary – all that is apparent is that mental health and substance use disorders are both present and exacerbating each other. The most important strategy in such cases is to intervene, stabilise the individual's mental state and gradually unravel cause and effect (Scott, Gilvarry, & Farrell, 1998).

Multiple studies have indicated that opioid substitution treatment can reduce levels of psychiatric distress with improvement apparent within weeks of commencement of treatment. All patients should be screened again for psychiatric disorders once stabilised on substitution treatment. A careful and detailed mental state examination will usually suffice.

Depression

Some symptoms of depression and anxiety, such as mood swings, feeling unable to deal with other people, lack of motivation, directly affect the ability to attend or participate in drug treatment (Holt, et al., 2007).

There is no clear evidence as to the effectiveness of antidepressants in conjunction with opioid substitution treatment for management of depression (Pani, Vacca, Trogu, Amato, & Davoli, 2010) . Enrolment and stabilisation in substitution treatment alone is likely to have a beneficial effect on psychiatric symptoms but depression will persist in 10-20% of patients treated with methadone (Nunes & Levin, 2004). Antidepressant treatment within opioid substitution treatment programs can improve depressive symptoms but robust effects in mood are not usual (A. R. Lingford-Hughes, et al., 2012). Buprenorphine may have advantages over methadone in treating opioid dependence in people with depression due to its kappa antagonist properties, although this has not been shown consistently (Dean, Bell, Christie, & Mattick, 2004; Gerra et al., 2006).

If antidepressants are to be used in combination with methadone or buprenorphine, then non-sedating antidepressants (such as SSRIs) are preferable to reduce the risk of overdose.

LINK

Appendix 3: Drug interactions

Drug interactions in 2.3.7

Cognitive-behavioural therapy in combination with pharmacotherapy may provide additional benefits in the treatment of depression in opioid users (Gordon, 2008).

It is theoretically possible for naltrexone to worsen mood, but recent studies have found naltrexone induction and/or maintenance to improve rather than worsen mood (Dean et al., 2006; Mysels, Cheng, Nunes, & Sullivan, 2011).

2 Treatment approaches in Australia

Anxiety

Opioids do not have anxiolytic effects in the way that benzodiazepines do, but they do have the ability to enable a person to forget about issues that may be causing them to feel anxious. In this way, short-term reduction in symptoms of anxiety may be a strong motivator for opioid use in those with anxiety disorders (Gordon, 2008).

Benzodiazepines are commonly misused, and the combination of benzodiazepines with opioid drugs, including methadone and buprenorphine, is a significant risk factor in overdose. Hence, the prescription of benzodiazepines to people who use opioid drugs should be approached with caution. If long-term benzodiazepine use is unable to be avoided, it should be monitored very closely (Gordon, 2008).

LINK

Overdose in 2.3.7

Appendix 3: Drug interactions

Drug interactions in 2.3.7

If treatment of anxiety with antidepressants is required in combination with methadone or buprenorphine, non-sedating antidepressants (e.g. SSRIs) should be preferred, taking into account interactions with methadone or buprenorphine.

Psychosis

The prevalence of comorbid psychosis and opioid use is generally low, but is associated with increased mortality. Concurrent opioid dependence and psychotic disorders are often associated with high levels of dysfunction (Gordon, 2008). People with schizophrenia typically have marked social impairment. They often have difficulty developing social relations and with resisting social pressure to use drugs; they also have difficulty developing the social support system needed to reduce use (Bellack & Gearon, 1998).

Schizophrenia is associated with a range of cognitive impairments that make it difficult for people with the illness to function well in substance abuse programs (Bellack & Gearon, 1998). Due to negative symptoms and side effects of medication, people with schizophrenia have great difficulty with taking the initiative and being self-motivated. Schizophrenia patients with substance use problems are generally unable to make and stand by definitive commitments to become abstinent. They need the ongoing support provided by programs that extend over time and are tolerant of patients dropping in and out, sometimes trying to quit and sometimes not (Bellack & Gearon, 1998).

Opioids (including methadone and buprenorphine) will exacerbate the sedative effects of antipsychotics, and some psychoactive medications, such as carbamazepine, will induce the metabolism of methadone and buprenorphine resulting in decreased plasma levels. There do not appear to be any interactions between naltrexone and antipsychotics (Gordon, 2008).

LINK

Appendix 3: Drug interactions

Early studies show onlanzapine, in combination with methadone or buprenorphine, may be effective in controlling opioid use and symptoms of psychosis (Gerra et al., 2007). Combined daily dispensing of psychotropic medication at the same time as daily dispensing of medications for MATOD may improve treatment compliance for the psychotic disorder (Gordon, 2008).

2 Treatment approaches in Australia

Personality disorders

People with personality disorder may have greater pre- and post-treatment problems, but they can improve as much as those without personality disorder. Hence drug and alcohol users with personality disorders probably benefit from standard treatments for substance use disorders (Alterman, Rutherford, Cacciola, McKay, & Boardman, 1998; Cacciola & Rutherford, 1996; Darke, Finlay-Jones, Kaye, & Blatt, 1996; A. R. Lingford-Hughes, et al., 2012).

Post-traumatic stress disorder

Exposure to trauma and post-traumatic stress disorder has been found to be highly prevalent among heroin dependent people in Australia (Mills, et al., 2005). Those with PTSD present with a more severe clinical profile compared to those with opioid dependence alone.

Treating PTSD and substance use separately can also be problematic given that the disorders may be functionally inter-related. Integrated treatment is probably to be preferred (Stewart, Pihl, Conrod, & Dongier, 1998).

2.6.7 Polydrug use

Polydrug use, or the use of multiple different drugs, is very common, particularly in treatment populations. Differentiation of the way in which drugs are used is worthwhile as it may point to effective management approaches. Patterns of use include:

- using a combination of drugs to produce a particular effect (for example, a more powerful sedative effect from a combination of an opioid and a benzodiazepine);
- use of one drug to reduce the adverse effects of another (e.g. use of cannabis or alcohol to reduce anxiety and other adverse consequences of methamphetamine);
- use of one drug to ameliorate withdrawal from another (e.g. use of benzodiazepines to relieve alcohol or opioid withdrawal);
- indiscriminate use of multiple drugs to produce intoxication (this is more common amongst younger drug users);
- concurrent dependence on two or more drugs (this may be associated with a strong predisposition to drug dependence arising from genetic, psychological and social factors).

Patients at high risk from polydrug use:

- frequently present intoxicated or with signs of benzodiazepine or alcohol withdrawal;
- regularly use other drugs at levels above normal therapeutic doses.

At the time of their entry to treatment, service providers need to be aware that patients may develop significant new alcohol and drug use habits that are potentially harmful whilst receiving treatment for opioid dependence. Some patients mistakenly believe that once on methadone, buprenorphine or naltrexone they will not develop other drug dependencies. This view should be addressed at induction and service providers should be alert to the possible development of new dependencies, and the need for appropriate interventions with such patients. Practitioners should caution patients against use of these drugs, and should monitor drug use at each appointment. The risks and benefits of continuing treatment should be assessed when patients are abusing or dependent upon other drugs.

2 Treatment approaches in Australia

Polydrug use and substitution treatment

All opioid substitution treatments should be approached with caution in individuals using other drugs, particularly those likely to cause sedation such as alcohol, as well as benzodiazepines and antidepressants in doses outside the normal therapeutic range. Particular attention should be given to assessing the level of dependence on opioids, co-dependence on other drugs and overdose risk.

There is currently inadequate evidence to favour either methadone or buprenorphine for patients who use both opioids and other drugs. Either treatment is appropriate for the management of the opioid dependence (A. Lingford-Hughes & Nutt, 2003).

Hazardous alcohol consumption is common among substitution treatment patients; it is prudent to detect hazardous alcohol consumption patterns and intervene early, either by treating the patient or referring them on.

Alcohol consumption should be monitored by history, examination and where appropriate liver function tests and breath alcohol readings. Methadone should not be administered to a patient who presents noticeably intoxicated with alcohol or any other drug.

In co-occurring alcohol dependence, due to the significant management problems presented by this group, consideration should be given to concurrent disulfiram or acamprosate therapy. If disulfiram or acamprosate are used, a methadone liquid formulation that does not contain alcohol should be considered to reduce the risk of reactions.

In pharmacotherapy treatment there are significant concerns with drug interactions, particularly the use of sedative drugs in combination with opioid pharmacotherapies. This concurrent drug use carries risks of intoxication and overdose. Patients who are using alcohol or other non-opioid drugs in a potentially harmful way at the time of their entry to opioid substitution treatment should be counselled on the dangers of intoxication, the harms of polydrug use, including increased risk of overdose, and on ways to reduce or stop hazardous use of alcohol and other drugs. Patients at high risk from polydrug use frequently present intoxicated or with signs of benzodiazepine or alcohol withdrawal, or regularly use other drugs at levels above normal therapeutic doses.

Treating polydrug use

Patients may prefer to deal with one drug issue at a time, particularly if they are likely to experience withdrawal on cessation of each drug. However, clinical outcomes may be better if the totality of drug problems is addressed simultaneously. Furthermore, some treatment modalities, particularly inpatient treatment and residential rehabilitation, require abstinence from all drugs. Even when treating people on an outpatient basis, encouragement should be given to addressing all forms of problematic drug use simultaneously. Evidence suggests that the use of a drug may precipitate relapse in an individual who is attempting to abstain from another drug. For example, in someone who is dependent on opioids, use of cannabis may increase risk of relapse to opioid use.

2 Treatment approaches in Australia

Psychological treatment and general counselling are often more effective if they address the patient's multiple drug problems simultaneously. Focusing on one drug problem to the exclusion of others can result in limited improvement in the patient's functioning despite a reduction in drug use. In addition, insights gained by a patient from CBT and other interventions can be applied simultaneously to multiple forms of drug use.

There may be advantages in cost and time saved, better outcomes and health benefits in treating all problems simultaneously if a patient is willing.

Smoking cessation treatment

The use of tobacco accounts for greater morbidity than alcohol and all other drugs combined. Among individuals treated for alcohol dependence, tobacco-related diseases were responsible for half of all deaths, greater than alcohol-related causes. In a 24-year study of long-term alcohol drinkers, the death rate among cigarette smokers was four times that of non-smokers. Although the magnitude of the problem of tobacco use in the population of opioid dependent people is clear, questions of when and how to best intervene remain (Bowman et al., 2012; J. J. Prochaska, Delucchi, & Hall, 2004). Recent studies suggest that, for at least some substances, simultaneous tobacco cessation reduces relapse rate (Reid et al., 2008). Interactions between opioid drugs and nicotine may help to explain high smoking rates in people receiving opioid substitution treatment (A. K. Elkader, Brands, Selby, & Sproule, 2009) and point to advantages from addressing use of both substances.

In a randomised controlled trial (Reid, et al., 2008), patients from methadone maintenance programs and outpatient drug and alcohol treatment received treatment as usual with or without adjunct smoking cessation treatment. Smoking cessation treatment comprised 8 weeks group counselling plus nicotine replacement patches. Smoking cessation treatment resulted in significant reductions in daily smoking and modest smoking abstinence rates without having an adverse impact on rehabilitation. The rates of smoking abstinence achieved (10% during treatment and 5-6% at the 3- and 6-month follow-up points) were considerably lower than those typically observed in the general population (30-50% during treatment and 10-20% at long-term follow-up). Many of the patients in this trial were established patients of long tenure – it remains possible that aggressive treatment of smoking at the outset of a course of drug and alcohol treatment could have negative impacts. This study also used a smoking cessation approach with high level group counselling. The authors noted that the time demands deterred some potential participants and could be a barrier to wider implementation of this type of program.

A systematic review of the effectiveness of smoking cessation interventions with individuals in addictions treatment or recovery (J. J. Prochaska, et al., 2004) found a significant increase in smoking abstinence among participants who received a smoking cessation intervention, with stronger effects associated with nicotine replacement therapy. (Psychosocial smoking cessation interventions were provided in 14 of 15 studies included in the systematic review, and 11 studies provided nicotine replacement therapy.) At long-term (6 months or more) follow-up, intervention effects were no longer significant. That is, the findings indicated good success at stopping smoking but difficulty with maintaining long-term cessation.

2 Treatment approaches in Australia

The relative difference between intervention and control conditions was similar for participants in addictions treatment and recovery. Cessation rates, however, were consistently higher among participants in recovery versus current addictions treatment (J. J. Prochaska, et al., 2004).

Among individuals in addictions treatment, smoking cessation interventions were associated with a significant increase in long-term sobriety relative to the control condition. This finding was taken to suggest that smoking cessation interventions may help with long-term sobriety even if long-term smoking cessation is not achieved (J. J. Prochaska, et al., 2004).

Because all treatments for smoking cessation appear equally effective and have few adverse effects, smokers should be informed of the pros and cons of the different treatments, and the use of one or more medication and psychosocial approaches recommended. If a smoker fails to quit, the reasons why relapse occurred should be assessed and then a more intense treatment, or a new treatment, or both, attempted. Combining medications and psychosocial treatments increases quit rates. Non-daily smokers are less likely to be nicotine dependent and are less likely to benefit from medications. Those with other drug problems are unlikely to quit unless these problems are treated prior to or along with the quit attempts, and may be at greater risk of relapse (Hughes, 2008).

Benzodiazepines

Benzodiazepine users exhibit overall patterns of increased risk and poorer psychological functioning than other patients.

LINK

Overdose section in 2.3.7

The association between benzodiazepine use and increased risk of overdose and increased risk of road traffic accidents (Bramness, Skurtveit, Morland, & Engeland, 2012; Leung, 2011) point to the importance of addressing misuse of benzodiazepines, particularly in combination with opioid drugs.

Caution should be exercised in prescribing benzodiazepines to people in opioid substitution treatment. The clinical supervision of patients receiving maintenance benzodiazepines must be of the same high standard as for opioid substitution treatment.

2.6.8 Infections in injecting drug users

Injecting drug users have a significant risk of infection from using unclean injecting equipment, particularly equipment that has been used by others, and injecting in unclean settings. Infections can be transmitted not only by needles and syringes but also swabs, filters, mixing spoons/water and tourniquets. Hepatitis C is the virus most frequently caught, but there is also a risk of catching hepatitis B and HIV/AIDS.

Bacterial and/or fungal infections can occur even when clean injecting equipment is used, particularly from injection of medications that have been placed in the mouth. Such infections may cause a local abscess at the injecting site or more seriously may cause infections in the heart (endocarditis) or other parts of the body. Damage to veins can occur from repeated injecting at the same site.

2 Treatment approaches in Australia

Clean needle programs and other open access services are important measures to reduce the risks of infection but treatment services should also be providing information on the risks of injecting use and approaches to reduce these risks.

Voluntary testing for HIV, hepatitis C and common infectious diseases should be encouraged as part of an individual assessment, accompanied by counselling before and after the test. Given Australia's proximity to countries in South-East Asia where there is high prevalence of HIV among people who inject drugs, patients should be strongly encouraged to undergo HIV testing. Serology testing and vaccination for hepatitis B is also recommended. TB and sexually transmitted diseases should also be considered during assessment (WHO, 2009). Where possible, testing should be provided within drug and alcohol clinics to optimise the likelihood of linkage to post-test interventions.

Opioid substitution treatment has demonstrated effectiveness in the prevention of infectious diseases, especially HIV/AIDS (L. Gowing, et al., 2011) but is also beneficial in promoting compliance with treatment regimens for HIV infections and tuberculosis (Batki, Gruber, Bradley, Bradley, & Delucchi, 2002; Malta, Strathdee, Magnanini, & Bastos, 2008; Spire, Lucas, & Carrieri, 2007) and is associated with better outcomes from treatment for these conditions (Antela et al., 1997; Moreno et al., 2001; Roux et al., 2009).

HIV/AIDS

Treatment programs should provide or refer HIV positive patients to specialist HIV medical facilities, so that their health may be appropriately monitored. HIV positive patients receiving opioid substitution treatment may need adjustment of their medication, particularly methadone, due to the potential for interactions between methadone and HIV medications and the effects of related illnesses, such as depression and tuberculosis.

LINK

Appendix 3
Drug interactions

Generally, patients who are HIV antibody positive are able to cope with the routine and conditions of pharmacotherapy treatment, but the medical, psychological and social implications of HIV/AIDS may require some flexibility in the arrangements for ongoing treatment. Where partners or carers of patients with HIV/AIDS have also had a history of injecting drug use, additional support may be required.

Hepatitis A and B

Hepatitis A virus is primarily transmitted through the faecal-oral route. Outbreaks occur more easily in overcrowded areas where poor sanitary conditions exist. Outbreaks of hepatitis A have also been reported among injecting drug users.

High-risk sexual behaviours and injection drug use are the major risk factors for hepatitis B transmission.

All patients on methadone, buprenorphine or naltrexone who are found to have no immunity to the hepatitis A or B viruses should be encouraged to have, or be offered, hepatitis A and B vaccinations. Consideration should also be given to recommending or offering vaccination to the sero-negative partners and close family contacts of patients who are hepatitis B sero-positive and potentially infectious. There are currently four hepatitis A vaccines and two combined hepatitis A/hepatitis B vaccines registered for use in Australia. Patients who are chronically infected with hepatitis B should be referred to a gastroenterologist for specialist assessment and follow-up. Approximately 90% of adults infected with hepatitis B will clear the virus, but 5-10% will become chronically infected and will require active management.

These tests are not mandatory prior to initiating treatment, and may be better undertaken during the first month of treatment.

2 Treatment approaches in Australia

Hepatitis C

The spread of hepatitis C virus (HCV) through injecting drug use is a major public health concern. In testing for HCV it is justifiable to determine not only the HCV antibody status, but also the HCV genotype and viral load, as this information will assist in post-test discussions about treatment outcomes.

Approximately 75% of people with HCV develop chronic infection which can lead to long-term liver damage. Current estimates are that 7% of people with chronic HCV infection will develop liver cirrhosis after 20 years infection, whilst 20% will develop cirrhosis after 40 years infection, indicating that disease progression is slow and therefore early intervention is paramount. Following development of cirrhosis, between two and five percent of people will develop liver failure and one to two percent liver cancer per annum[21]. With the increasing age of opioid users, mortality from long-term hepatitis C and its complications is increasing.

The high prevalence of HCV in patients of drug treatment services represents a substantial pool of infection. Increasing participation of these patients in HCV treatment would have significant public health benefits. The aim of treatment is to prevent the development of liver failure and liver cancer. The combination of pegylated interferon-a and ribavirin is now the standard of care for chronic HCV. With this treatment rates of sustained virological remission are around 40 to 50 percent for genotype 1 and 80% for genotypes 2 and 3. However, the addition of boceprevir or telaprevir to the treatment regimen is associated with a higher likelihood of remission in genotype 1 infections (Chou et al., 2013), and these two medications are now included on the Pharmaceutical Benefits Scheme. Treatment response in injecting drug users with HCV is similar to non-injecting drug users (Sullivan & Fiellin, 2004). Furthermore, medication adherence and treatment outcomes may be improved when treatment for HCV is linked with drug and alcohol treatment (Stein et al., 2012).

Encouraging uptake of HCV treatment presents significant challenges. Treatment involves a lengthy time commitment (usually 6 or 12 months) and can result in unpleasant side effects and lifestyle disruption. Given that many people with HCV are asymptomatic for a long period of time, the decision to enter into a treatment regimen which may significantly impact on their lifestyle can be difficult. It is important that people with HCV are provided with accurate information regarding the benefits of treatment and the possible negative impacts that treatment may have. In addition, people undergoing HCV treatment should be provided with adequate support and counselling services to assist the management of side effects and encourage treatment compliance. It is important that health care providers are aware of HCV treatment options and appropriate referral pathways for eligible patients.

Strong links should be established between drug and alcohol clinical services and liver clinics where treatment can be offered.

Where an individual has been infected with hepatitis C it is important to ascertain their hepatitis B status as co-infection with hepatitis B may cause the illness to be more aggressive and treatment involving interferon will require more detailed monitoring.

[21] *HIV, viral hepatitis and STIs: A guide for primary care*. Australasian Society for HIV Medicine (2008). Available from http://www.ashm.org.au.

2 Treatment approaches in Australia

Education and counselling should be offered to explain the consequences of hepatitis C infection and to reduce high-risk behaviour and minimise the spread of the virus. Information should include advice on reduction in hazardous use of all drugs (including alcohol) and the management of ill health due to hepatitis C. Patients should be advised against sharing injecting equipment (including tourniquets, spoons and solvents), as well as razors, toothbrushes or other instruments which may be vehicles for the exchange of blood.

Patients with chronic liver disease on long-term substitution treatment generally do not need dose alterations but abrupt changes in liver function might necessitate substantial dose adjustments.

2.6.9 Prisoners

In many cases prisoners discontinue or significantly reduce their drug use when entering prison, but the drug use that occurs is typically more risky (Hedrich et al., 2012; Stallwitz & Stover, 2007). In the South Australian setting between 13-14% of metropolitan intake prisoners use opioids in a high risk manner. Over 50% of prisoners report injecting drug use in the three months prior to prison entry (Holmwood, Marriott, & Humeniuk, 2008).

Because correctional systems have high turnover rates and re-incarceration rates, inmate health also profoundly affects the health of the communities to which they return. Inmates' transitions back to their communities are often associated with increased health risks, particularly increased sexual and drug-related risks. Relapse to substance use is common amongst people with a history of substance use following release from prison, and is associated with increased criminal activity, risk of HIV and HCV infection, drug overdose, death from drug-related overdose, and reincarceration.

These issues identify this patient group as one that warrants special consideration, the aims being to increase well-being and social functioning following release, as well as to reduce the risks to community safety and health.

Release from prison is a time of high overdose risk for opioid users due to their reduced tolerance to opioids developed during imprisonment (Stallwitz & Stover, 2007). The provision of opioid substitution treatment during imprisonment and pre-release, and the provision of advice in relation to the higher risk of overdose is important to reduce this risk (Cropsey et al., 2011; Hedrich, et al., 2012).

The post-release phase of the treatment process has been found to be of critical importance in reducing the risk of relapse and further criminal activity among prisoners with drug dependence problems. Several studies show that effective aftercare is essential to maintaining the gains made in prison-based treatment of drug dependence. In addition to drug dependence treatment needs, many ex-prisoners have housing and financial difficulties and in some instances psychiatric problems. They may be released to either poor family support or deeply dysfunctional families and friends. For this reason, aftercare cannot be limited to drug treatment but needs to include social support services (Jurgens, 2007). Appropriate liaison between correctional centres and health services needs to be undertaken to ensure continuity of treatment for those released from prison (Hedrich, et al., 2012).

2 Treatment approaches in Australia

2.6.10 Management of pain

Acute pain in patients receiving pharmacotherapies for opioid dependence

For mild pain, non-opioid analgesics (aspirin, paracetamol, NSAIDs) should be used. Patients taking naltrexone will not benefit from opioid-containing medications such as cough, cold and anti-diarrhoeal preparations.

Where additional opioid analgesia is required for moderate pain, increasing the dose of methadone or buprenorphine may be appropriate for a limited time.

Substitution treatment patients admitted to hospital should have their methadone or buprenorphine treatment continued if possible. Methadone maintenance patients who are not allowed oral intake, as may occur after abdominal surgery, should be given parenteral opioid analgesia, preferably by continuous infusion in doses adequate to provide pain relief and control withdrawal. Once able they should be recommenced on oral methadone and continue with parenteral opioid for analgesia, progressively reducing the dose.

Due to their tolerance of opioids, substitution treatment patients will require larger doses of analgesia for adequate pain relief. The dose and route of administration should be discussed with practitioners with appropriate expertise in pain management. Drugs with mixed agonist/antagonist opioid properties or partial agonists such as buprenorphine should not be administered to methadone-maintained patients as they may precipitate an acute withdrawal syndrome.

There is evidence of cross tolerance between methadone and anaesthetic agents – patients on methadone may require higher doses of anaesthetic agents in the event of dental or surgical procedures. Patients being admitted for major surgery should advise their doctors that they are taking buprenorphine or methadone and discuss pain management options for the postoperative period prior to surgery. Naltrexone should be discontinued at least 72 hours before elective surgery including dental surgery, if it is anticipated that opioid analgesia may be required. The treating practitioner should be informed that the patient has been taking naltrexone. The patient should then be abstinent from the opioid for three to five days before resuming naltrexone treatment, depending on the duration of the opiate use and the half-life of the opiate. A more conservative approach is to wait seven days.

LINK

A7.6 Management of pain

Chronic pain

The co-occurrence of pharmaceutical opioid dependence and severe chronic pain poses significant challenges for patients, families and carers, health practitioners and health systems. Many patients experience poorly co-ordinated and inadequate treatment, stigma (from family, friends, the community and health providers), and these in-turn can further impair treatment outcomes and overall quality of life for the patient. The following provides an overview of the key principles in the management of such patients.

2 Treatment approaches in Australia

Assessment and diagnosis

The following issues should be taken into account.

1. Pain condition: etiology, severity, site, precipitating and relieving factors.
2. Opioid use: history of opioid use, current patterns of use, amount, frequency, route, withdrawal profile, tolerance, attempts at opioid cessation or reduction, psychosocial criteria of dependence; side effects and other adverse events with opioids.
3. Other substance use: past and current history of other substance use.
4. Aberrant drug behaviours including:
   - source of medications (number of doctors attended, over the counter opioid use, friends and relatives, street/black market supplies);
   - routes of drug use, including history of injecting complications;
   - frequency, extent and factors related to dose escalations;
   - chemical coping (opioid use for reasons other than severe pain such as sleep, anxiety).
5. Other strategies for responding to pain: use and effectiveness of approaches, including
   - physical therapies (e.g. exercise, physiotherapy, acupuncture, TENS etc);
   - psychological approaches (CBT, relaxation approaches);
   - non-opioid medications.
6. Mental health, particularly mood disorders, previous and current treatment, either pharmacological or psychosocial.
7. Physical health, including conditions related to pain disorder, opioid and other substance use (e.g. side effects to opioids, injecting related harms). Investigate accordingly (including sex hormone and polysomnograph, ECG testing as indicated).
8. Social circumstances, including relationships, employment, legal and financial conditions.
9. Family history of pain disorders, substance use.
10. Identify concerns of patient and others (family, employers, other health professionals) regarding opioid use. Systematically explore:
    - opioid-related side effects,
    - impaired pain outcomes (related to opioid withdrawal, hyperalgesia, over-reliance upon opioids without use of other dimensions to pain management),
    - aberrant behaviours (see 4 above)
11. Assess patient motivation to address opioid dependence within broader pain management plan.

2 Treatment approaches in Australia

Management plan

The first step in planning is to identify therapeutic goals and conditions for opioid use.

Negotiate with patient and document realistic goals regarding the management of chronic pain and of opioid treatment within a broader pain management plan (including the 5As: Analgesia, Activities, Affect, Adverse events and Aberrant behaviours). Identify how these will be assessed and monitored – include:

- self-monitoring (e.g. diaries);
- assessment scales (e.g. BPI, K-10);
- aberrant behaviours (pill counts, urine drug screens, prescription monitoring systems, examination of injecting sites);
- collateral reports (communication with other doctors, pharmacists, relatives).

Include family and carers in the identification of treatment goals and treatment plans.

Document the patient 'contract', identifying conditions of opioid treatment, how treatment will be monitored, and repercussions of persistent aberrant behaviours.

Rationalise medications

Opioid medication should be rationalised within the context of the broader pain management plan.

1. Identify and coordinate service providers involved in the patient's care, including who has responsibility for prescribing, dispensing and monitoring opioid, other psychoactive and non-opioid adjuvant pain medications.
2. Rationalise and structure opioid treatment – identify which opioid(s), dose and frequency of use, and frequency of dispensing.
3. Use long acting or sustained released opioid medications and medications with a lower risk of misuse and diversion where available. Avoid short-acting opioids and injected preparations where possible.
4. Use structured regimens and minimise 'prn' use of opioid medication.
5. Patients with a history of multiple dose escalations, overdoses, diversion or injection of medications should have supervised dosing and/or frequent interval dispensing (e.g. daily, three times a week or weekly).
6. Patient requiring high opioid doses (greater than 120mg oral morphine equivalent per day) should be reviewed by a pain and/or addiction specialist.
7. Consider a trial of conventional opioid analgesics (morphine, oxycodone, fentanyl patches, hydromorphine, oral methadone tablets) if there is no recent history of significant aberrant drug behaviours (e.g. injecting, diversion, overdoses), with frequent review and monitoring. If there is a recent history of significant aberrant behaviours (diversion, injecting, overdoses) or the patient is likely to be unable to adhere to a treatment plan with conventional opioid analgesics, select between methadone oral liquid and high dose sublingual buprenorphine or buprenorphine-naloxone (see Figure 5). Both oral methadone and high dose sublingual buprenorphine are effective opioid analgesics, and have the added benefits of enabling closer supervision, monitoring and structure to opioid treatment. Consult with pain and/or addiction medicine specialists regarding choice of medications and transfer between opioid medications. For patients who do not benefit from, or are unable to adhere to and opioid treatment plan, consider attempting opioid withdrawal.

2 Treatment approaches in Australia

8. Opioid rotation: there is limited controlled evidence for the role of opioid rotation, however there is considerable clinical experience suggesting it may have a role for some patients using high doses (tolerance) of a particular opioid, and who may benefit from a rotation to another opioid. The role of opioid rotation should be discussed with a pain specialist for a particular patient.
9. Rationalise other psychoactive medications, particularly use of benzodiazepines or other sedatives that can lower safety threshold of opioids, and medications with drug-drug interactions with opioid medications (e.g. CYP inducers/inhibitors and impact upon methadone metabolism; QTc prolonging medications)
10. Ensure compliance with relevant jurisdictional regulatory requirements regarding S8 medications, including notification /permits for opioid medications.

LINK

A4.4.5 Drug interactions

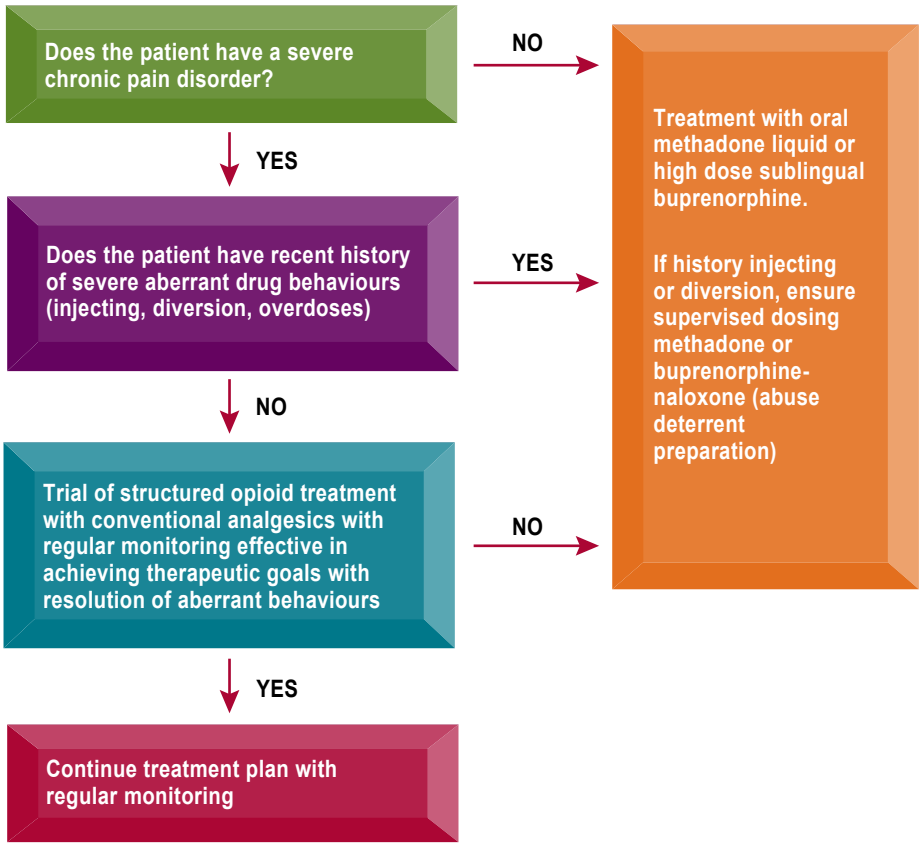
2.3.7 Adverse effects

Appendix 3: Drug interactions

Maintain accurate documentation

Documentation should identify the broader pain management plan addressing pain (physical therapies, psychological approaches, adjuvant medications) and other co-morbidities (e.g. addressing mental health, other substance use, medical and social co-morbidities). Strategies for dealing with 'break through' or acute exacerbations of pain should also be documented.

Figure 5: Choice of opioid preparations in managing patients dependent on pharmaceutical opioids



2 Treatment approaches in Australia

2.6.11 Other health issues

Sleep disturbances

Sleep disturbance is common in people who use drugs, including during withdrawal and recovery from drug dependence.

Patients on methadone appear to be at increased risk of sleep apnoea and the use of hypnotic drugs may, paradoxically, worsen sleep by exacerbating sleep apnoea. Chronic pain and misuse of benzodiazepines are associated with poor sleep, regardless of the methadone dose (E. Peles, Schreiber, & Adelson, 2009).

LINK

Benzodiazepines in 2.6.7

Overdose in 2.3.7

One study has reported that naltrexone has fewer adverse effects on sleep than methadone (Staedt et al., 1996), but despite this many patients complain of insomnia, particularly on initiation of naltrexone treatment.

Additional medications, particularly benzodiazepines, should be avoided if possible, because of the risk of misuse and association with increased risk of overdose. Provide patients with information on non-pharmacological approaches to improving sleep, including sleep hygiene and simple relaxation techniques.

Driving

Both methadone and buprenorphine are known to have central nervous system effects that impact on the ability to drive safely (Corsenac et al., 2012; Soyka et al., 2008). However, with chronic dosing tolerance develops, to various extents, to the central nervous system effects (Soyka, et al., 2008) and early epidemiological studies found no substantial difference in motor vehicle accident risk between methadone maintenance patients and controls. This is the basis of the position taken in previous guidelines that patients on stable doses of methadone or buprenorphine can safely drive (Lenne, et al., 2003), but during induction or dose changes, patients should be advised not to drive or use machinery.

A recent systematic review (Strand, Fjeld, Arnestad, & Mørland, 2013) found an increased risk of traffic accident involvement for both methadone and buprenorphine patients, and unclear findings from experimental studies regarding impairments of cognitive and psychomotor functions. Multiple factors, in addition to tolerance, can potentially affect the capacity to drive, including use of methadone or buprenorphine, dose, and use of alcohol or other drugs (Bramness, et al., 2012; Leung, 2011). Hence, a view on fitness to drive needs to be based on assessment of individual patients (Schisler, Groninger, & Rosielle, 2012; Shmygalev et al., 2011).

Buprenorphine appears to be associated with less impairment but there is some risk of bias in studies comparing buprenorphine and methadone reducing the strength of this conclusion.

Dental problems

All opioids, including methadone and buprenorphine, reduce the production of saliva while uncontrolled use is associated with poor nutrition and poor dental hygiene. Hepatitis C may further reduce saliva production via induction of Sjorgen's syndrome. Consequently dental problems are common at entry to substitution treatment. It is common for patients to blame substitute medications for their dental problems.

Salivary flow can be increased by chewing gum. Encourage patients to improve dental hygiene.

3 Supporting Information

Quality framework

3.1 Assessment and treatment engagement

The purpose of assessment is to identify patients' needs, determine their suitability for treatment and establish a treatment plan. A thorough assessment should precede all treatment and should involve comprehensive drug use, medical and psychosocial history, physical and mental state examination and, as clinically indicated, other appropriate investigations.

Good assessment is essential to the continuing care of the patient. Not only can it enable the patient to become engaged in treatment but it can begin a process of change even before a full assessment is complete.

The effectiveness of treatment can be expected to be greater if treatment is responsive to an individual's stage of change and personal circumstance. Good care planning aims to deliver services that are patient-centred rather than centred on the service provider (National Treatment Agency for Substance Misuse, 2002). Care plans can facilitate patient access to an integrated selection of services and may prevent patient drop out. Assessment is the first stage of care planning.

The primary purpose of assessment is to carry out a functional analysis and determine the best type of response (UNODC, 2003). However, the initial assessment is also a time when patient and clinician establish a therapeutic relationship. Hence the content and manner of assessment are both important.

The general principles of assessment discussed in this section are applicable to all forms of treatment for alcohol and other drug use. The nature of opioid substitution treatment places some additional requirements on assessment of eligibility for this form of treatment.

3.2 Establishing and defining a therapeutic relationship

For the prospective patient, the assessment interview is often a time of great vulnerability and expectation. The decision to seek treatment is frequently taken at a time of crisis. Many patients feel ambivalent about treatment, particularly substitution treatment, and entering treatment may be marked by a sense of failure and guilt.

It is important for clinicians to demonstrate an accepting, non-judgmental approach to patients, being neither authoritarian nor overly intrusive.

Patients are often hesitant or reluctant to disclose their drug use or problems. Patients who are addicted report discomfort, shame, fear, distrust, hopelessness, and the desire to continue using drugs as reasons they do not discuss addiction openly with their clinicians.

Clinicians need to approach patients who have an addiction in an honest, respectful way, just as they would approach patients with any other medical illness or problem.

3 Quality framework

It is important for clinicians to employ common sense, courtesy and an appropriate level of neutrality in establishing a relationship with patients. It is easy to present the impression of being excessively distant, remote and authoritarian in order to protect oneself from the demands and manipulations of the patient. At the other extreme it is also easy for the prescriber to become overly sympathetic to the patient and too accepting of the patient's own account of their circumstances. In this situation doctors may come to see themselves as advocates and supporters of their patients to the extent of becoming enmeshed in what is happening to them.

It is probably more beneficial for patients in the long term if the doctor preserves appropriate neutrality: being concerned and caring but also recognising when patients are making excessive demands and not rescuing them from their often self-induced crises.

The therapeutic relationship should be based upon mutual understanding between doctor and patient of:

- their respective views as to the cause and nature of the patient's problems;
- each party's expectations of treatment – what doctor expects of patient, patient of doctor and patient of treatment;
- how the patient's goals might best be met.

The more overt and collaborative the approach to treatment and the more responsibility for treatment is shared, the more effective the treatment is likely to be.

Suggested elements which improve an effective assessment:

- Ability to establish a helping alliance
- Good interpersonal skills
- Non-possessive warmth
- Friendliness
- Genuineness
- Respect
- Empathy
- Supportive style
- Patient-centred approach
- Reflective listening

Despite their ambivalence to treatment, patients may appear preoccupied with whether and when they will be allowed to receive methadone or buprenorphine, if this is an option. Such focusing on access to the drug is characteristic of drug dependence. Unless this issue is dealt with fairly early in the interview, it is difficult to establish any rapport. Once opioid dependence is confirmed, the patient can be reassured about their eligibility for substitution treatment and issues such as treatment alternatives, side effects of substitution treatment and program rules and procedures can be discussed more meaningfully.

3 Quality framework

At the initial interview, in order to ensure their access to treatment, particularly substitution treatment, some patients will say whatever they think their doctor wants to hear. For this reason, it is not often advisable to set specific treatment goals at the initial interview, as patients tend to nominate unrealistic expectations of what they will achieve from treatment.

Assessment is an ongoing process, and gaining a psychosocial history from the patient does not stop at the first interview. The assessment interview is also the time for setting the ground rules.

Prescribers of methadone and buprenorphine have considerable power in the relationship with their patients. This can cause problems, particularly with a patient who is vulnerable or who has difficulty with authority figures. It is important to handle this power differential sensitively, avoiding adversarial relationships with patients who resent their perceived powerlessness in regard to program rules.

More importantly doctors must strive to avoid exploiting the doctor–patient relationship. Emotional exploitation can occur by prescribers taking an intrusive and voyeuristic interest in the often colourful details of the patient's lifestyle and experiences.

Most patients are willing and able to provide reliable, factual information regarding their drug use.

Questions should be asked in a direct and straightforward manner, using simple language and avoiding street terms.

Using open-ended questions will elicit more information than simple, closed-ended, "yes" or "no" or single-answer questions, examples:

- How has heroin use affected your life?
- How has heroin affected your life?
- In the past, what factors have helped you stop using?
- What specific concerns do you have today?
- How often do you use heroin?
- When was the last time you were using heroin?
- How many times did you use last month?

In general, at assessment or in the first weeks of treatment, clinicians should ensure that physical health and psychological functioning have been assessed, either by themselves or by referral. Specific screening for HIV, hepatitis B and C and for psychiatric illness is recommended. Some of these issues may be dealt with at the assessment interview, while others may be more appropriately attended to once the patient has been stabilised in treatment.

3 Quality framework

3.3 Treatment planning

All structured treatments should be delivered according to a written, individual treatment plan for each patient. Planning should be a collaborative process and involve an assessment with the patient, not of the patient. Plans should take into account the views and motivations of the patient and their personal and social supports and problems (National Treatment Agency for Substance Misuse, 2006; UNODC, 2003).

The aims of care planning are to (National Treatment Agency for Substance Misuse, 2002):

- Develop, manage and review documented care plans;
- Ensure that patients with problematic substance use have access to a comprehensive range of services across local drug treatment systems;
- Ensure the coordination of care across all agencies involved with the service user;
- Ensure that there is continuity of care and that patients are followed throughout their contact with the treatment system;
- Maximise patient retention within the treatment system and minimise the risk of patients losing contact with the treatment and care services;
- Re-engage patients who have dropped out of the treatment system;
- Avoid duplication of assessment and interventions; and
- Prevent patients 'falling between services'.

A treatment plan should (UNODC, 2003):

- Describe the patient and their personal, social, economic and legal situation;
- Show sensitivity and awareness of the patient's culture, ethnic background and religious affiliation as well as their gender and sexuality;
- Describe the patient's current problems (as known at intake);
- Specify authorised sharing of information (what information will be sought and/or given to other professionals/agencies and under what circumstances);
- Describe the specific interventions that are planned;
- Set out the goals of treatment and progress 'milestones' that can be achieved;
- Describe how the care plan will be reviewed over time.

The care plan concept reflects the fact that many people have continuing care needs even when a treatment episode has been completed. It also acknowledges that individuals enter the treatment system at different points and can travel across the treatment system over time (UNODC, 2003).

Treatment agreements need to be flexible and realistic. It is important that patients do not take on goals they are unlikely to reach as their failure to reach them may destabilise their progress in treatment.

3 Quality framework

Plans should include negotiated goals that are:

- Patient directed;
- Respectful of the patient's stage of change;
- Clear
- Realistic and achievable

Goals in treatment need to be short-term. This may be achieved by breaking down larger problems into smaller tasks for action or change. This makes the management and resolution of large problems more feasible and gives patients a sense of achievement and greater control.

Goals could include:

- Reduction in drug use;
- Improved physical health;
- Improved psychological health;
- Improved social adjustment and functioning;
- Reduction in harm associated with drug use; and
- Reduction in criminal behaviour.

The smaller tasks/goals should meet the following criteria:

- Desirable
- Evaluable
- Positive
- Specific in time frame
- Achievable
- Measurable

Realistic treatment agreements can provide the treatment process with a sense of structure and purpose beyond the daily routine.

3.4 Case management or care coordination

Case management or care coordination is key to an integrated, effective treatment program (UNODC, 2003). A case manager or care coordinator:

- develops, manages and reviews documented care plans based on ongoing assessment (including risk assessment);
- ensures that the care plan takes account of the patient's ethnicity, gender and sexuality;
- advises other professionals also involved in the treatment plan of any known changes in circumstances of the patient that may require a review or change of the care arrangements;
- carries out an early follow-up of discharged patients (where feasible); and
- seeks to re-engage people who have dropped out of the treatment system.

3 Quality framework

The level or intensity of care coordination required will reflect the nature of the patient's current problem. A "standard case management" level of response would be envisaged for patients who require treatment from a single treatment modality, are relatively stable, and pose little danger to themselves or others.

In contrast, a "multifaceted care coordination" model, of higher support and intensity of care, would be more appropriate for patients who have:

- Multiple needs that cannot be provided successfully by one service provider;
- Multiple needs but are only willing to engage with one agency;'
- Contact with a number of agencies at referral;
- A severe comorbidity;
- The potential for harm to themselves or others.

3.5 Reviewing treatment progress

LINK

Appendix 9: ATOP

Reviews of treatment progress benefit both clinician and patient by highlighting areas of progress, or relapse, and indicating the need for adjustment of the treatment plan. Instruments that are available and useful in the assessment of treatment response include the ATOP, the CRA goal planner[22], and the Treatment Effectiveness Assessment (Walter Ling, et al., 2012).

Because people often leave treatment prematurely, and premature departure is associated with high rates of relapse to drug use, programs need strategies to engage and keep patients in treatment. These strategies should be part of the treatment review process.

A major goal of treatment is to reduce unsanctioned drug use and drug dependency. Hence, monitoring the use of opioids and other drugs is an important component of treatment programs. Such monitoring is of value in evaluating the overall effectiveness of a particular program and its individual treatment providers. For example if there is a high proportion of patients using heroin or other psychoactive drugs in hazardous ways this may indicate an aspect of treatment needs to be changed.

In substitution treatment the chief concern of concurrent drug use is safety – patients taking methadone, and to a lesser extent buprenorphine, with high doses of other CNS depressants are vulnerable to overdoses, which can be lethal.

Monitoring may be useful in determining how well patients are progressing in treatment and whether changes in treatment should be made for patients with specific problems. Monitoring can also be used to support contingency management approaches.

Monitoring patients' drug use can give useful information for making informed decisions on clinical management, particularly with regards to patient safety from concurrent use of other drugs with substitute medications, and provide a basis for program evaluation. However, there is little evidence to support the use of drug monitoring as a deterrent against unsanctioned drug use and drug-positive results should not be used punitively. This is an area requiring great skill as often interventions that are seen as response to risk by clinicians (such as reduction or diminution of unsupervised doses) will be seen as punitive by the patient.

[22] See http://www.nta.nhs.uk/uploads/itep_routes_to_recovery_part4_240309.pdf. Accessed 4 April 2013.

3 Quality framework

Current monitoring options used widely include urine testing, patient self-reporting and clinical observation. The validity and reliability of these techniques can be improved when used in conjunction with one another.

Self-reporting although a subjective measure, is relatively unobtrusive and can be a useful indicator of episodes of patients' drug use when used in certain settings (Darke, 1998). Self-report can be a reliable guide to drug use in settings where no negative consequences result from disclosure. Self-reporting is also conducive to facilitating an atmosphere of trust and good-will between staff and patients. However, caution should be exercised when making clinical decisions based solely on self-reported drug use.

Urine testing should only be undertaken with good reason, such as in the initial clinical assessment of individual patients or as part of program evaluation. Urine testing can also be useful when patients are unstable (such as in the early stages of pharmacotherapy) and when there is some uncertainty about their drug use. There is little evidence to support the use of urine drug monitoring as a deterrent against unsanctioned drug use. Test results should be used, in collaboration with the patient, to review and improve the individual's progress in treatment.

Urinalysis will only detect recent drug use. The actual time frame varies depending on the drug being measured and will also depend on the threshold level set by the testing laboratory.

LINK

Appendix 7: Detection times for selected drugs in urine

Clinical observation is also an important part of monitoring treatment progress. Useful indicators include signs of drug use, frequency of contacts, missed appointments and missed doses of medication.

Where treatment goals are not being met, a review of treatment strategies should occur, including:

- the role of psychosocial interventions;
- levels of supervision, monitoring and review;
- dose of the substitution opioid;
- the role of adjuvant interventions, and – ultimately –
- a review of alternative opioid pharmacotherapies. For example, patients who cannot stabilise their continued use of other opioids, even on high doses of buprenorphine, may be better suited to treatment with high doses of a full agonist such as methadone.

The extent to which patients are required to, or do in fact wish to, reduce or eliminate consumption of illegal drugs is one of the most critical and divisive issues in opioid substitution treatment. The goal of eliminating all illegal drug use, especially in the first few months of treatment, is unrealistic and very likely to impede treatment progress and patient–clinician rapport.

3 Quality framework

3.6 Records and reporting

Case records detailing patient's clinical history and progress in treatment should be established and adequately maintained.

Jurisdictions may set minimal standards for case records. These standards should cover content, quality, confidentiality, security and access.

It should be noted that records can be accessed through legal means, such as the serving of subpoenas, and that while a service may seek to restrict the public use of the records, this cannot be guaranteed.

There should be clear and concise notes, properly signed, named and dated. A separate structured sheet for recording prescribing must be kept. A patient-held record, countersigned by those involved in care, can be a useful adjunct to treatment.

The following items of data are considered important components of a minimum dataset, to be collected and assessed by service providers on an ongoing basis.

- Number of patients registered in treatment broken down by:
  - site of treatment
  - age;
  - gender (male, female);
  - employment status (including sickness allowance, disability , pension, sole parent pension, job etc, as separate categories);
  - proportion of patients entering treatment for the first time ever, readmissions, continuing treatment.
- Retention in treatment:
  - Mean duration
- Average dose of methadone or buprenorphine
- Death rates:
  - number of deaths from all causes, of patients in active treatment at the time of death, during the reporting year and the proportion that are opioid related.

Each jurisdiction will be responsible for central monitoring and regulation of methadone and buprenorphine prescribing.

The Australian Government will be responsible for collating national treatment data with respect to methadone and buprenorphine, and this data will be collected and provided to the Australian Government by jurisdictions.

3 Quality framework

Jurisdictions should collect data on an annual basis on the number of patients registered in buprenorphine and methadone treatment, broken down by:

- treatment sector for prescribing (public prescriber, private prescriber and prison medical services);
- nature of medication prescribed; and
- nature of dosing points (public clinics, private clinics, community pharmacies and correctional facilities).

Every contact between the health service and the patient should be recorded in the patient's case record. The case records should be up to date and clearly legible.

Documentation should include:

- personal details (including verification of identity);
- social and family situation;
- drug use history (including alcohol, illegal and prescribed drugs, current medications);
- history of prior drug and alcohol treatment;
- other evidence of dependence;
- medical history, including psychiatric illness;
- findings of assessments;
- outline of treatment plan, including any agreed goals for treatment established during initial or subsequent assessments.

Case records should reveal a comprehensive assessment and document each interaction between service provider and patient, including the periodic reviews of the patient's progress. Case records are confidential and must be held securely.

References

Abbott, P. J. (2009). A review of the community reinforcement approach in the treatment of opioid dependence. *Journal of Psychoactive Drugs, 41*(4), 379-385.

Abrahams, R. R., Kelly, S. A., Payne, S., Thiessen, P. N., Mackintosh, J., & Janssen, P. A. (2007). Rooming-in compared with standard care for newborns of mothers using methadone or heroin. *Canadian Family Physician, 53*(10), 1722-1730.

Adi, Y., Juarez-Garcia, A., Wang, D., Jowett, S., Frew, E., Day, E., . . . Burls, A. (2007). Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation. *Health Technology Assessment, 11*(6), 1-85.

Ahmadi, J. (2002). A randomized, clinical trial of buprenorphine maintenance treatment for Iranian patients with opioid dependency. *Addictive Disorders & Their Treatment, 1*(1), 25-27.

Ahmadi, J., & Ahmadi, M. (2003). Twelve-month maintenance treatment of heroin-dependent outpatients with buprenorphine. *Journal of Substance Use, 8*(1), 39-41.

Alterman, A. I., Rutherford, M. J., Cacciola, J. S., McKay, J. R., & Boardman, C. R. (1998). Prediction of 7 months methadone maintenance treatment response by four measures of antisociality. *Drug and Alcohol Dependence, 49*(3), 217-223.

Amass, L., Bickel, W. K., Crean, J. P., Blake, J., & Higgins, S. T. (1998). Alternate-day buprenorphine dosing is preferred to daily dosing by opioid-dependent humans. *Psychopharmacology, 136*(3), 217-225.

Amass, L., Bickel, W. K., Higgins, S. T., & Badger, G. J. (1994). Alternate-day dosing during buprenorphine treatment of opioid dependence. *Life Sciences, 54*(17), 1215-1228.

Amass, L., Bickel, W. K., Higgins, S. T., & Hughes, J. R. (1994). A preliminary investigation of outcome following gradual or rapid buprenorphine detoxification. *Journal of Addictive Diseases, 13*(3), 33-45.

Amass, L., Kamien, J. B., & Mikulich, S. K. (2000). Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine-naloxone tablet. *Drug and Alcohol Dependence, 58*(1-2), 143-152.

Amass, L., Kamien, J. B., & Mikulich, S. K. (2001). Thrice-weekly supervised dosing with the combination buprenorphine-naloxone tablet is preferred to daily supervised dosing by opioid-dependent humans. *Drug and Alcohol Dependence, 61*(2), 173-181.

Amass, L., Pukeleviciene, V., Subata, E., Almeida, A. R., Pieri, M. C., D'Egidio, P., . . . Strang, J. (2011). A prospective, randomized, multicenter acceptability and safety study of direct buprenorphine/naloxone induction in heroin-dependent individuals. *Addiction, 107*, 142-151.

Amato, L., Davoli, M., Minozzi, S., Ferroni, E., Ali, R., & Ferri, M. (2013). Methadone at tapered doses for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews*(2). doi: 10.1002/14651858.CD003409.pub3.

Amato, L., Minozzi, S., Davoli, M., & Vecchi, S. (2011a). Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database of Systematic Reviews, 9*, CD005031.

Amato, L., Minozzi, S., Davoli, M., & Vecchi, S. (2011b). Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database of Systematic Reviews*(10). doi: 10.1002/14651858.CD004147.pub4

Anchersen, K., Clausen, T., Gossop, M., Hansteen, V., & Waal, H. (2009). Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. *Addiction, 104*(6), 993-999.

Antela, A., Casado, J. L., Gonzalez, M. J., Perez, P., Perez-Elias, M. J., Montilla, P., & Buzon, L. (1997). Influence of a methadone maintenance programme on the improved outcome of a cohort of injecting drug users with advanced HIV disease. *AIDS, 11*(11), 1405-1406.

R References

Baca, C. T., & Grant, K. J. (2005). Take-home naloxone to reduce heroin death. *Addiction, 100*(12), 1823-1831.

Baker, A., Gowing, L., Lee, N. K., & Proudfoot, H. (2004). Psychosocial interventions. In A. Baker, N. K. Lee & L. Jenner (Eds.), *Models of intervention and care for psychostimulant users* (pp. 63-84). Canberra: Commonwealth of Australia.

Bakstad, B., Sarfi, M., Welle-Strand, G. K., & Ravndal, E. (2009). Opioid maintenance treatment during pregnancy: Occurrence and severity of neonatal abstinence syndrome. *European Addiction Research, 15*(3), 128-134.

Ball, J. C., Lange, W. R., Myers, C. P., & Friedman, S. R. (1988). Reducing the risk of AIDS through methadone maintenance treatment. *Journal of Health and Social Behavior, 29*(3), 214-226.

Batki, S. L., Gruber, V. A., Bradley, J. M., Bradley, M., & Delucchi, K. (2002). A controlled trial of methadone treatment combined with directly observed isoniazid for tuberculosis prevention in injection drug users. *Drug and Alcohol Dependence, 66*(3), 283-293.

Bauer, C. R., Shankaran, S., Bada, H. S., Lester, B., Wright, L. L., Krause-Steinrauf, H., . . . Verter, J. (2002). The Maternal Lifestyle Study: Drug exposure during pregnancy and short-term maternal outcomes. *American Journal of Obstetrics and Gynecology, 186*(3), 487-495.

Bearn, J., Gossop, M., & Strang, J. (1999). Rapid opiate detoxification treatments. *Drug and Alcohol Review, 18*(1), 75-81.

Becker, A. B., Strain, E. C., Bigelow, G. E., Stitzer, M. L., & Johnson, R. E. (2001). Gradual dose taper following chronic buprenorphine. *American Journal on Addictions, 10*(2), 111-121.

Bell, J. (1998). Delivering effective methadone treatment. In J. Ward, R. P. Mattick & W. Hall (Eds.), *Methadone Maintenance Treatment and Other Opioid Replacement Therapies* (pp. 161-175). Amsterdam: Harwood Academic Publishers.

Bell, J., Chan, J., & Kuk, A. (1995). Investigating the influence of treatment philosophy on outcome of methadone maintenance. *Addiction, 90*(6), 823-830.

Bellack, A. S., & Gearon, J. S. (1998). Substance abuse treatment for people with schizophrenia. *Addictive Behaviors, 23*(6), 749-766.

Berghella, V., Lim, P. J., Hill, M. K., Cherpes, J., Chennat, J., & Kaltenbach, K. (2003). Maternal methadone dose and neonatal withdrawal. *American Journal of Obstetrics and Gynecology, 189*(2), 312-317.

Binder, T., & Vavrinková, B. (2008). Prospective randomised comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birthweight of newborns, early postpartum adaptation and course of the neonatal abstinence syndrome (NAS) in women followed up in the outpatient department. *Neuroendocrinology Letters, 29*(1), 80-86.

Bisaga, A., Sullivan, M. A., Cheng, W. Y., Carpenter, K. M., Mariani, J. J., Levin, F. R., . . . Nunes, E. V. (2011). A placebo controlled trial of memantine as an adjunct to oral naltrexone for opioid dependence. *Drug and Alcohol Dependence, 119*, e23-e29.

Bond, A. J., Reed, K. D., Beavan, P., & Strang, J. (2012). After the randomised injectable opiate treatment trial: Post-trial investigation of slow-release oral morphine as an alternative opiate maintenance medication. *Drug and Alcohol Review, 31*(4), 492-498.

Bowman, J., Wiggers, J., Colyvas, K., Wye, P., Walsh, R. A., & Bartlem, K. (2012). Smoking cessation among Australian methadone clients: Prevalence, characteristics and a need for action. *Drug and Alcohol Review, 31*(4), 507-513.

Boyd, J., Randell, T., Luurila, H., & Kuisma, M. (2003). Serious overdoses involving buprenorphine in Helsinki. *Acta Anaesthesiologica Scandinavica, 47*(8), 1031-1033.

Brahen, L. S., Henderson, R. K., Capone, T., & Kordal, N. (1984). Naltrexone treatment in a jail work-release program. *Journal of Clinical Psychiatry, 45*(9, Sec. 2), 49-52.

Bramness, J. G., Skurtveit, S., Morland, J., & Engeland, A. (2012). An increased risk of motor vehicle accidents after prescription of methadone. *Addiction, 107*, 967-972.

Brown, A. S., & Fleming, P. M. (1998). A naturalistic study of home detoxification from opiates using lofexidine. *Journal of Psychopharmacology, 12*(1), 93-96.

Brown, C. H., Bennett, M. E., Li, L., & Bellack, A. S. (2011). Predictors of initiation and engagement in substance abuse treatment among individuals with co-occurring serious mental illness and substance use disorders. *Addictive Behaviors, 36*(5), 439-447.

R References

Brown, R. T., & Zueldorff, M. (2007). Opioid substitution with methadone and buprenorphine: Sexual dysfunction as a side effect of therapy. *Heroin Addiction & Related Clinical Problems, 9*(1), 35-44.

Bukten, A., Skurtveit, S., Gossop, M., Waal, H., Stangeland, P., Havnes, I., & Clausen, T. (2012). Engagement with opioid maintenance treatment and reductions in crime: a longitudinal national cohort study. *Addiction, 107*(2), 393-399.

Burns, L., Mattick, R. P., Lim, K., & Wallace, C. (2007). Methadone in pregnancy: treatment retention and neonatal outcomes. *Addiction, 102*(2), 264-270.

Burns, L., Randall, D., Hall, W. D., Law, M., Butler, T., Bell, J., & Degenhardt, L. (2009). Opioid agonist pharmacotherapy in New South Wales from 1985 to 2006: patient characteristics and patterns and predictors of treatment retention. *Addiction, 104*(8), 1363-1372.

Cacciola, J. S., & Rutherford, M. (1996). Personality disorders and treatment outcome in methadone maintenance patients. *Journal of Nervous and Mental Disease, 184*(4), 236-239.

Cami, J., Gilabert, M., San, L., & de la Torre, R. (1992). Hypercortisolism after opioid discontinuation in rapid detoxification of heroin addicts. *British Journal of Addiction, 87*(8), 1145-1151.

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.

Chiang, C. N., & Hawks, R. L. (2003). Pharmacokinetics of the combination tablet of buprenorphine and naloxone. *Drug and Alcohol Dependence, 70*(Suppl), S39-S47.

Chou, R., Hartung, D., Rahman, B., Wasson, N., Cottrell, E. B., & Fu, R. (2013). Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: A systematic review. *Annals of Internal Medicine, 158*, 114-123.

Christo, G., & Franey, C. (1995). Drug users' spiritual beliefs, locus of control and the disease concept in relation to Narcotics Anonymous attendance and six-month outcomes. *Drug and Alcohol Dependence, 38*, 51-56.

Clark, N. C., Lintzeris, N., & Muhleisen, P. J. (2002). Severe opiate withdrawal in a heroin user precipitated by a massive buprenorphine dose. *Medical Journal of Australia, 176*(4), 166-167.

Cleary, B. J., Donnelly, J., Strawbridge, J., Gallagher, P. J., Fahey, T., Clarke, M., & Murphy, D. J. (2010). Methadone dose and neonatal abstinence syndrome - systematic review and meta-analysis. *Addiction, 105*(12), 2071-2084.

Cleary, B. J., Reynolds, K., Eogan, M., O'Connell, M. P., Fahey, T., Gallagher, P. J., . . . Murphy, D. J. (2013). Methadone dosing and prescribed medication use in a prospective cohort of opioid-dependent pregnant women. *Addiction, 108*, 762-770.

Cleaver, H., Unell, I., & Aldgate, J. (2011). *Children's Needs - Parenting Capacity* (2nd ed.). London, UK: TSO (The Stationery Office).

Comer, S. D., Collins, E. D., & Fischman, M. W. (2001). Buprenorphine sublingual tablets: effects on IV heroin self-administration by humans. *Psychopharmacology, 154*(1), 28-37.

Comer, S. D., Sullivan, M. A., Yu, E., Rothenberg, J. L., Kleber, H. D., Kampman, K., . . . O'Brien, C. P. (2006). Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Archives of General Psychiatry, 63*(2), 210-218.

Conway, K. P., Compton, W., Stinson, F. S., & Grant, B. F. (2006). Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry, 67*(2), 247-257.

Cook, C. C. H. (1988). The Minnesota Model in the Management of Drug and Alcohol Dependency: miracle, method or myth? Part I. The Philosophy and the Programme. *British Journal of Addiction, 83*, 625-634.

Copeland, J., Gerber, S., & Swift, W. (2006). *Evidence-based answers to cannabis questions: a review of the literature*. Canberra: Australian National Council on Drugs.

R References

Copello, A., Orford, J., Hodgson, R., Tober, G., & Barrett, C. (2002). Social behaviour and network therapy: Basic principles and early experiences. *Addictive Behaviors, 27*, 345-366.

Copello, A., Williamson, E., Orford, J., & Day, E. (2006). Implementing and evaluating Social Behaviour and Network Therapy in drug treatment practice in the UK: A feasibility study. *Addictive Behaviors, 31*, 802-810.

Cornish, R., Macleod, J., Strang, J., Vickerman, P., & Hickman, M. (2010). Risk of death during and after opiate substitution treatment in primary care: Prospective observational study in UK General Practice Research Database. *BMJ, 341*, c5475.

Corsenac, P., Lagarde, E., Gadegbeku, B., Delorme, B., Tricotel, A., Castot, A., . . . Orriols, L. (2012). Road traffic crashes and prescribed methadone and buprenorphine: A French registry-based case-control study. *Drug and Alcohol Dependence, 123*, 91-97.

Cousins, G., Teljeur, C., Motterlini, N., McCowan, C., Dimitrov, B. D., & Fahey, T. (2011). Risk of drug-related mortality during periods of transition in methadone maintenance treatment: A cohort study. *Journal of Substance Abuse Treatment, 41*, 252-260.

Coyle, M. G., Salisbury, A. L., Lester, B. M., Jones, H. E., Lin, H., Graf-Rohrmeister, K., & Fischer, G. (2012). Neonatal neurobehavior effects following buprenorphine versus methadone exposure. *Addiction, 107*(Suppl 1), 63-73.

Croop, R. S., Faulkner, E. B., & Labriola, D. F. (1997). The safety profile of naltrexone in the treatment of alcoholism. *Archives of General Psychiatry, 54*, 1130-1135.

Cropsey, K. L., Lane, P. S., Hale, G. J., Jackson, D. O., Clark, C. B., Ingersoll, K. S., . . . Stitzer, M. L. (2011). Results of a pilot randomized controlled trial of buprenorphine for opioid dependent women in the criminal justice system. *Drug and Alcohol Dependence, 119*, 172-178.

Cushman, P. (1974). Detoxification of rehabilitated methadone patients: frequency and predictors of long-term success. *American Journal of Drug and Alcohol Abuse, 1*(3), 393-408.

D'Ippoliti, D., Davoli, M., Perucci, C. A., Pasqualini, F., & Bargagli, A. M. (1998). Retention in treatment of heroin users in Italy: the role of treatment type and of methadone maintenance dosage. *Drug and Alcohol Dependence, 52*, 167-171.

Darke, S. (1998). Self-report among injecting drug users: a review. *Drug and Alcohol Dependence, 51*(3), 253-263.

Darke, S., Finlay-Jones, R., Kaye, S., & Blatt, T. (1996). Anti-social personality disorder and response to methadone maintenance treatment. *Drug and Alcohol Review, 15*, 271-276.

Darke, S., McDonald, S., Kaye, S., & Torok, M. (2012). Comparative patterns of cognitive performance amongst opioid maintenance patients, abstinent opioid users and non-opioid users. *Drug and Alcohol Dependence, 126*(3), 309-315.

Darke, S., Mills, K. L., Ross, J., & Teesson, M. (2011). Rates and correlates of mortality amongst heroin users: Findings from the Australian Treatment Outcome Study (ATOS), 2001-2009. *Drug and Alcohol Dependence, 115*(3), 190-195.

Darke, S., Ross, J., Mills, K. L., Williamson, A., Havard, A., & Teesson, M. (2007). Patterns of sustained heroin abstinence amongst long-term, dependent heroin users: 36 months findings from the Australian Treatment Outcome Study (ATOS). *Addictive Behaviors, 32*(9), 1897-1906.

Day, E. (2012). Commentary on Nosyk *et al.* (2012): Detoxification from methadone maintenance therapy: how important is the exact technique that is used? *Addiction, 107*, 1630-1631.

Day, E., Ison, J., & Strang, J. (2008). Inpatient versus other settings for detoxification for opioid dependence. *Cochrane Database of Systematic Reviews*(4). doi: 10.1002/14651858.CD004580.pub2

Dean, A. J., Bell, J., Christie, M. J., & Mattick, R. P. (2004). Depressive symptoms during buprenorphine vs. methadone maintenance: findings from a randomised, controlled trial in opioid dependence. *European Psychiatry, 19*(8), 510-513.

Dean, A. J., Saunders, J. B., Jones, R. T., Young, R. M., Connor, J. P., & Lawford, B. R. (2006). Does naltrexone treatment lead to depression? Findings from a randomized controlled trial in subjects with opioid dependence. *Journal of Psychiatry and Neuroscience, 31*(1), 38-45.

Degenhardt, L., Larance, B. K., Bell, J. R., Winstock, A. R., Lintzeris, N., Ali, R. L., . . . Mattick, R. P. (2009). Injection of medications used in opioid substitution treatment in Australia after the introduction of a mixed partial agonist–antagonist formulation. *MJA, 191*, 161-165.

R References

Degenhardt, L., Randall, D., Hall, W., Law, M., Butler, T., & Burns, L. (2009). Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug and Alcohol Dependence, 105*(1-2), 9-15.

Des Jarlais, D. C., Friedman, S. R., Woods, J., & Milliken, J. (1992). HIV infection among intravenous drug users: Epidemiology and emerging public health perspectives. In J. H. Lowinson, P. Ruiz, R. B. Millman & J. G. Langrod (Eds.), *Substance Abuse: A Comprehensive Textbook* (2nd ed., pp. 734-743). Baltimore: Williams & Wilkins.

DiClemente, C. C., Nidecker, M., & Bellack, A. S. (2008). Motivation and the stages of change among individuals with severe mental illness and substance abuse disorders. *Journal of Substance Abuse Treatment, 34*(1), 25-35.

Doran, C., Holmes, J., Ladewig, D., & Ling, W. (2005). Buprenorphine induction and stabilisation in the treatment of opiate dependence. *Heroin Addiction & Related Clinical Problems, 7*(1), 7-18.

Doris, J. L., Meguid, V., Thomas, M., Blatt, S., & Eckenrode, J. (2006). Prenatal cocaine exposure and child welfare outcomes. *Child Maltreatment, 11*(4), 326-337.

Drummond, D. C. (2001). Theories of drug craving, ancient and modern. *Addiction, 96*, 33-46.

Dunlop, A., Petroulias, D., Marope, D., Khoo, K., Kimber, J., Ritter, A., . . . Osborn, D. A. (2009). Pharmacotherapies and pregnancy. In R. P. Mattick, R. Ali & N. Lintzeris (Eds.), *Pharmacotherapies for Opioid Dependence Treatment* (pp. 282-329). London, UK: Informa Healthcare.

Dunn, C., Deroo, L., & Rivara, F. P. (2001). The use of brief interventions adapted from motivational interviewing across behavioral domains: a systematic review. *Addiction, 96*(12), 1725-1742.

Dyer, K. R. (2005). Methadone maintenance treatment and mood disturbances: Pharmacological and psychological implications. *Heroin Addiction & Related Clinical Problems, 7*(2), 5-10.

Dyer, K. R., & White, J. M. (1997). Patterns of symptom complaints in methadone maintenance patients. *Addiction, 92*(11), 1445-1455.

Eap, C. B., Buclin, T., & Baumann, P. (2002). Interindividual variability of the clinical pharmacokinetics of methadone. *Clinical Pharmacokinetics, 41*(14), 1153-1193.

Egli, N., Pina, M., Christensen, P. S., Aebi, M., & Killias, M. (2009). Effects of drug substitution programs on offending among drug-addicts. *Campbell Systematic Reviews, 3*.

Eissenberg, T., Greenwald, M. K., Johnson, R. E., Liebson, I. A., Bigelow, G. E., & Stitzer, M. L. (1996). Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans. *Journal of Pharmacology and Experimental Therapeutics, 276*(2), 449-459.

el-Guebaly, N. (2012). The meanings of recovery from addiction: evolution and promises. *Journal of Addiction Medicine, 6*(1), 1-9.

Elkader, A., & Sproule, B. (2005). Buprenorphine: Clinical pharmacokinetics in the treatment of opioid dependence. *Clinical Pharmacokinetics, 44*(7), 661-680.

Elkader, A. K., Brands, B., Selby, P., & Sproule, B. A. (2009). Methadone-nicotine interactions in methadone maintenance treatment patients. *Journal of Clinical Psychopharmacology, 29*(3), 231-238.

Faggiano, F., Vigna-Taglianti, F., Versino, E., & Lemma, P. (2003). Methadone maintenance at different dosages for opioid dependence. *Cochrane Database of Systematic Reviews*(3). doi: 10.1002/14651858.CD002208

Fajemirokun-Odudeyi, O., Sinha, C., Tutty, S., Pairaudeau, P., Armstrong, D., Phillips, T., & Lindow, S. W. (2006). Pregnancy outcome in women who use opiates. *European Journal of Obstetrics, Gynecology, and Reproductive Biology, 126*(2), 170-175.

Faroqui, M. H., Cole, M., & Curran, J. (1983). Buprenorphine, benzodiazepines and respiratory depression. *Anaesthesia, 38*(10), 1002-1003.

Ferri, M., Davoli, M., & Perucci, C. A. (2011). Heroin maintenance for chronic heroin-dependent individuals. *Cochrane Database of Systematic Reviews*(12). doi: 10.1002/14651858.CD003410.pub4

Fiorentine, R., & Hillhouse, M. P. (2000). Self-efficacy, expectancies, and abstinence acceptance: further evidence for the addicted-self model of cessation of alcohol- and drug-dependent behaviour. *American Journal of Drug and Alcohol Abuse, 26*(4), 497-521.

R References

Fischer, G., Gombas, W., Eder, H., Jagsch, R., Peternell, A., Stuhlinger, G., . . . Kasper, S. (1999). Buprenorphine versus methadone maintenance for the treatment of opioid dependence. *Addiction, 94*(9), 1337-1347.

Flynn, P. M., & Brown, B. S. (2008). Co-occurring disorders in substance abuse treatment: Issues and prospects. *Journal of Substance Abuse Treatment, 34*(1), 36-47.

Forrest, A. L. (1983). Buprenorphine and lorazepam. *Anaesthesia, 38*(6), 598.

Fudala, P. J., Jaffe, J. H., Dax, E. M., & Johnson, R. E. (1990). Use of buprenorphine in the treatment of opioid addiction. II. Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. *Clinical Pharmacology and Therapeutics, 47*(4), 525-534.

Gaalema, D. E., Scott, T. L., Heil, S. H., Coyle, M. G., Kaltenbach, K., Badger, G. J., . . . Jones, H. E. (2012). Differences in the profile of neonatal abstinence syndrome signs in methadone- versus buprenorphine-exposed neonates. *Addiction, 107*(Suppl 1), 53-62.

Gal, T. J. (1989). Naloxone reversal of buprenorphine-induced respiratory depression. *Clinical Pharmacology and Therapeutics, 45*(1), 66-71.

Galanter, M. (2006). Spirituality in Alcoholics Anonymous: A valuable adjunct to psychiatric services. *Psychiatric Services, 57*(3), 307-309.

Gaulier, J. M., Charvier, F., Monceaux, F., Marquet, P., & Lachatre, G. (2004). Ingestion of high-dose buprenorphine by a 4 year-old child. *Journal of Toxicology - Clinical Toxicology, 42*(7), 993-995.

Gerra, G., Di Petta, G., D'Amore, A., Ianotta, P., Bardicchia, F., Falorni, F., . . . Zaimovic, A. (2007). Combination of olanzapine with opioid-agonists in the treatment of heroin-addicted patients affected by comorbid schizophrenia spectrum disorders. *Clinical Neuropharmacology, 30*(3), 127-135.

Gerra, G., Leonardi, C., D'Amore, A., Strepparola, G., Fagetti, R., Assi, C., . . . Lucchini, A. (2006). Buprenorphine treatment outcome in dually diagnosed heroin dependent patients: a retrospective study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 30*(2), 265-272.

Gerstein, D. R., Johnson, R. A., Harwood, H. J., Fountain, D., Suter, N., & Malloy, K. (1994). *Evaluation Recovery Services: The California drug and alcohol treatment assessment (CALDATA)*. Sacramento, California: Department of Alcohol and Drug Programs.

Giacomuzzi, S., Haaser, W., Pilsz, L., & Riemer, Y. (2005). Driving impairment on buprenorphine and slow-release oral morphine in drug-dependent patients. *Forensic Science International, 152*(2-3), 323-324.

Gibson, J. C., & Vulliamy, A. (2010). Accidental methadone poisoning in children: a call for Canadian research action. *Child Abuse and Neglect, 34*(8), 553-554.

Gjersing, L., Waal, H., Caplehorn, J. R. M., Gossop, M., & Clausen, T. (2010). Staff attitudes and the associations with treatment organisation, clinical practices and outcomes in opioid maintenance treatment. *BMC Health Services Research, 10*, 194.

Gonzalez, J. P., & Brogden, R. N. (1988). Naltrexone: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. *Drugs, 35*, 192-213.

Gordon, A. (2008). Comorbidity of mental disorders and substance use: A brief guide for the primary care clinician. *National Drug Strategy Monograph Series, 71*. Retrieved from http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/Content/mono71

Gossop, M. (2011). Treating drug misuse problems: evidence of effectiveness. London, UK: National Treatment Agency for Substance Misuse. Retrieved from www.nta.nhs.uk

Gossop, M., Griffiths, P., Bradley, B., & Strang, J. (1989). Opiate withdrawal symptoms in response to 10 day and 21 day methadone withdrawal programmes. *British Journal of Psychiatry, 154*, 360-363.

Gossop, M., Marsden, J., Stewart, D., & Rolfe, A. (2000). Patterns of improvement after methadone treatment: 1 year follow-up results from the National Treatment Outcome Research Study (NTORS). *Drug and Alcohol Dependence, 60*, 275-286.

Gossop, M., & Strang, J. (1997). Rapid anaesthetic-antagonist detoxification of heroin addicts: What origins, evidence and clinical justification? *British Journal of Intensive Care, 7*(2), 66-69.

R References

Gourarier, L., Lowenstein, W., Gisselbrecht, M., Chauveau, J. M., Haas, C., & Durand, H. (1996). [Withdrawal syndrome in 2 drug addicts after intravenous injection of buprenorphine?] Syndrome de manque chez deux toxicomanes apres injection intraveineuse de buprenorphine? *Presse Medicale, 25*(27), 1239-1240.

Gowing, L., Ali, R., & White, J. (2009a). Buprenorphine for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews*(3). doi: 10.1002/14651858.CD002025.pub3

Gowing, L., Ali, R., & White, J. M. (2009b). Opioid antagonists with minimal sedation for opioid withdrawal. *Cochrane Database of Systematic Reviews*(4). doi: 10.1002/14651858.CD002021.pub3

Gowing, L., Ali, R., & White, J. M. (2010). Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. *Cochrane Database of Systematic Reviews*(1). doi: 10.1002/14651858.CD002022.pub3

Gowing, L., Farrell, M., Bornemann, R., Sullivan, L., & Ali, R. (2011). Substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database of Systematic Reviews*(8). doi: 10.1002/14651858.CD004145.pub2

Gowing, L., Proudfoot, H., Henry-Edwards, S., & Teesson, M. (2001). *Evidence supporting treatment: the effectiveness of interventions for illicit drug use*. Canberra: Australian National Council on Drugs.

Gowing, L. R., & Ali, R. L. (2006). The place of detoxification in treatment of opioid dependence. *Current Opinion in Psychiatry, 19*(3), 266-270.

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

Greenwald, M. K. (2002). Heroin craving and drug use in opioid-maintained volunteers: Effects of methadone dose variations. *Experimental and Clinical Psychopharmacology, 10*(1), 39-46.

Grella, C. E., & Lovinger, K. (2011). 30-Year trajectories of heroin and other drug use among men and women sampled from methadone treatment in California. *Drug and Alcohol Dependence, 118*, 251-258.

Groh, D. R., Jason, L. A., & Keys, C. B. (2008). Social network variables in alcoholics anonymous: A literature review. *Clinical Psychology Review, 28*, 430-450.

Groshkova, T., Best, D., & White, W. (2013). The assessment of recovery capital: Properties and psychometrics of a measure of addiction recovery strengths. *Drug and Alcohol Review, 32*, 187-194.

Gruber, V. A., Delucchi, K. L., Kielstein, A., & Batki, S. L. (2008). A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug and Alcohol Dependence, 94*(1-3), 199-206.

Hall, K., Gibbie, T., & Lubman, D. I. (2012). Motivational interviewing techniques: Facilitating behaviour change in the general practice setting. *Australian Family Physician, 41*(9), 660-667.

Hall, W. (1996). Methadone maintenance treatment as a crime control measure. *Crime and Justice Bulletin*(29).

Hall, W., Ward, J., & Mattick, R. P. (1998). The effectiveness of methadone maintenance treatment 1: Heroin use and crime. In J. Ward, R. P. Mattick & W. Hall (Eds.), *Methadone Maintenance Treatment and Other Opioid Replacement Therapies* (pp. 17-57). Amsterdam: Harwood Academic Publishers.

Harris, D. S., Mendelson, J. E., Lin, E. T., Upton, R. A., Jones, R. T., Harris, D. S., . . . Jones, R. T. (2004). Pharmacokinetics and subjective effects of sublingual buprenorphine, alone or in combination with naloxone: Lack of dose proportionality. *Clinical Pharmacokinetics, 43*(5), 329-340.

Harrison, C. A., & Abou Saleh, M. T. (2002). Psychiatric disorders and substance misuse: psychopathology. In G. H. Rassool (Ed.), *Dual diagnosis: Substance misuse and psychiatric disorders* (pp. 43-57). Oxford: Blackwell Science.

Hartzler, B., Lash, S. J., & Roll, J. M. (2012). Contingency management in substance abuse treatment: A structured review of the evidence for its transportability. *Drug and Alcohol Dependence, 122*(1-2), 1-10.

R References

Hedrich, D., Alves, P., Farrell, M., Stover, H., Moller, L., & Mayet, S. (2012). The effectiveness of opioid maintenance treatment in prison settings: a systematic review. *Addiction, 107*, 501-517.

Heinz, A., Beck, A., Grusser, S. M., Grace, A. A., & Wrase, J. (2008). Identifying the neural circuitry of alcohol craving and relapse vulnerability. *Addiction Biology, 14*, 108-118.

Herve, S., Riachi, G., Noblet, C., Guillement, N., Tanasescu, S., Goria, O., . . . Lerebours, E. (2004). Acute hepatitis due to buprenorphine administration. *European Journal of Gastroenterology and Hepatology, 16*(10), 1033-1037.

Holmwood, C., Marriott, M., & Humeniuk, R. (2008). Substance use patterns in newly admitted male and female South Australian prisoners using the WHO-ASSIST (Alcohol, Smoking and Substance Involvement Screening Test). *International Journal of Prison Health, 4*(4), 198-207.

Holt, M., Treloar, C., McMillan, K., Schultz, M., & Bath, N. (2007). *Barriers and incentives to treatment for illicit drug users with mental health comorbidities and complex vulnerabilities*. Canberra: Commonwealth of Australia.

Horgan, J. (1989). Lukewarm turkey. *Scientific American, 260*(3), 32.

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*, 125-134.

Hughes, J. (2008). An algorithm for choosing among smoking cessation treatments. *Journal of Substance Abuse Treatment, 34*(4), 426-432.

Humeniuk, R., Ali, R., Babor, T., Souza-Formigoni, M. L. O., Boerngen de Lacerda, R., Ling, W., . . . Vendetti, J. (2012). A randomized controlled trial of a brief intervention for illicit drugs linked to the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in clients recruited from primary health-care settings in four countries. *Addiction, 107*, 957-966.

Humeniuk, R., Ali, R., McGregor, C., & Darke, S. (2003). Prevalence and correlates of intravenous methadone syrup administration in Adelaide, Australia. *Addiction*, 98(4), 413-418.

Humeniuk, R., Ali, R., White, J., Hall, W., & Farrell, M. (2000). *Proceedings of expert workshop on the induction and stabilisation of patients onto methadone*. Canberra, Australia: Commonwealth Department of Health and Aged Care.

Jacobs, E. A., & Bickel, W. K. (1999). Precipitated withdrawal in an opioid-dependent outpatient receiving alternate-day buprenorphine dosing. *Addiction, 94*(1), 140-141.

Jansson, L. M., Choo, R., Velez, M. L., Harrow, C., Schroeder, J. R., Shakleya, D. M., & Huestis, M. A. (2008). Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics, 121*, 106-114.

Jansson, L. M., Di Pietro, J. A., Elko, A., Williams, E. L., Milio, L., & Velez, M. (2012). Pregnancies exposed to methadone, methadone and other illicit substances, and poly-drugs without methadone: A comparison of fetal neurobehaviors and infant outcomes. *Drug and Alcohol Dependence, 122*(3), 213-219.

Jansson, L. M., Velez, M., & Harrow, C. (2009). The opioid-exposed newborn: assessment and pharmacologic management. *Journal of Opioid Management, 5*(1), 47-55.

Jasinski, D. R. (1981). Opiate withdrawal syndrome: acute and protracted aspects. *Annals of the New York Academy of Sciences, 362*, 183-190.

Jasinski, D. R., Haertzen, C. A., Henningfield, J. E., Johnson, R. E., Makhzoumi, H. M., & Miyasato, K. (1982). Progress report of the NIDA Addiction Research Center. *NIDA Research Monograph, 41*, 45-52.

Jaudes, P. K., Ekwo, E., & Van, V. J. (1995). Association of drug abuse and child abuse. *Child Abuse and Neglect, 19*(9), 1065-1075.

Johnson, R. E., Eissenberg, T., Stitzer, M. L., Strain, E. C., Liebson, I. A., & Bigelow, G. E. (1995). Buprenorphine treatment of opioid dependence: clinical trial of daily versus alternate-day dosing. *Drug and Alcohol Dependence, 40*(1), 27-35.

Johnson, R. E., Strain, E. C., & Amass, L. (2003). Buprenorphine: how to use it right. *Drug and Alcohol Dependence, 70*(Suppl. 2), S59-S77.

Jones, H. E., Heil, S. H., Baewert, A., Arria, A. M., Kaltenbach, K., Martin, P. R., . . . Fischer, G. (2012). Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review. *Addiction, 107*(Suppl 1), 5-27.

R References

Jones, H. E., Kaltenbach, K., Heil, S. H., & Stine, S. M. (2010). Neonatal abstinence syndrome after methadone or buprenorphine exposure. *New England Journal of Medicine, 363*(24), 2320-2331.

Jones, H. E., O'Grady, K. E., Malfi, D., & Tuten, M. (2008). Methadone maintenance vs. methadone taper during pregnancy: Maternal and neonatal outcomes. *American Journal on Addictions, 17*(5), 372-386.

Jurgens, R. (2007). Interventions to address HIV in prisons: Drug dependence treatments. Geneva: World Health Organization.

Kakko, J., Heilig, M., & Sarman, I. (2008). Buprenorphine and methadone treatment of opiate dependence during pregnancy: Comparison of fetal growth and neonatal outcomes in two consecutive case series. *Drug and Alcohol Dependence, 96*, 69-78.

Kakko, J., Svanborg, K. D., Kreek, M. J., & Heilig, M. (2003). 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet, 361*(9358), 662-668.

Kaltenbach, K., Berghella, V., & Finnegan, L. (1998). Opioid dependence during pregnancy: effects and management. *Obstetrics and Gynecology Clinics of North America, 25*(1), 139-152.

Kaltenbach, K., Holbrook, A. M., Coyle, M. G., Heil, S. H., Salisbury, A. L., Stine, S. M., . . . Jones, H. E. (2012). Predicting treatment for neonatal abstinence syndrome in infants born to women maintained on opioid agonist medication. *Addiction, 107*(Suppl 1), 45-52.

Kaskutas, L. A. (2009). Alcoholics Anonymous effectiveness: Faith meets science. *Journal of Addictive Diseases, 28*, 145-157.

Kaskutas, L. A., Zhang, L., French, M. T., & Witbrodt, J. (2005). Women's programs versus mixed-gender day treatment: results from a randomized study. *Addiction, 100*(1), 60-69.

Keene, J. (2005). A case-linkage study of the relationship between drug misuse, crime, and psychosocial problems in a total criminal justice population. *Addiction Research and Theory, 13*(5), 489-502.

Keene, J., Stenner, K., Connor, M., & Fenley, S. (2007). A case-study of substitute opiate prescribing for drug-using offenders. *Drugs: Education, Prevention & Policy, 14*(5), 443-456.

Kelly, J. F., Magill, M., & Stout, R. L. (2009). How do people recover from alcohol dependence? A systematic review of the research on mechanisms of behavior change in Alcoholics Anonymous. *Addiction Research & Theory, 17*(3), 236-259.

Kelly, S. M., Schwartz, R. P., O'Grady, K. E., Gandhi, D., & Jaffe, J. J. (2012). Impact of methadone with versus without drug abuse counseling on HIV risk: 4- and 12-month findings from a clinical trial. *Journal of Addiction Medicine, 6*(2), 145-152.

Knape, J. T. (1986). Early respiratory depression resistant to naloxone following epidural buprenorphine. *Anesthesiology, 64*(3), 382-384.

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology Reviews, 35*, 217-238.

Kornor, H., Waal, H., & Ali, R. L. (2006). Abstinence-orientated buprenorphine replacement therapy for young adults in out-patient counselling. *Drug & Alcohol Review, 25*(2), 123-130.

Kosten, T. R., Morgan, C., & Kleber, H. D. (1991). Treatment of heroin addicts using buprenorphine. *American Journal of Drug and Alcohol Abuse, 17*(2), 119-128.

Kosten, T. R., Rounsaville, B. J., & Kleber, H. D. (1985). Comparison of clinician ratings to self reports of withdrawal during clonidine detoxification of opiate addicts. *American Journal of Drug and Alcohol Abuse, 11*(1-2), 1-10.

Kosten, T. R., Schottenfeld, R., Ziedonis, D., & Falcioni, J. (1993). Buprenorphine versus methadone maintenance for opioid dependence. *Journal of Nervous and Mental Disease, 181*(6), 358-364.

Kreek, M. J. (2000). Methadone-related opioid agonist pharmacotherapy for heroin addiction. History, recent molecular and neurochemical research and future in mainstream medicine. *Annals of the New York Academy of Sciences, 909*, 186-216.

Kreek, M. J., Borg, L., Ducat, E., & Ray, B. (2010). Pharmacotherapy in the treatment of addiction: Methadone. *Journal of Addictive Diseases, 29*(2), 209-216.

R References

Krentzman, A. R., Robinson, E. A., Moore, B. C., Kelly, J. F., Laudet, A. B., White, W. L., . . . Strobbe, S. (2011). How Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) work: Cross-disciplinary perspectives. *Alcoholism Treatment Quarterly, 29*, 75-84.

Kroll, B. (2004). Living with an elephant: Growing up with parental substance misuse. *Child & Family Social Work, 9*(2), 129-140.

Kuhlman, J. J., Levine, B., Johnson, R. E., Fudala, P. J., & Cone, E. J. (1998). Relationship of plasma buprenorphine and norbuprenorphine to withdrawal symptoms during dose induction, maintenance and withdrawal from sublingual buprenorphine. *Addiction, 93*(4), 549-559.

Kunoe, N., Lobmaier, P., Vederhus, J. K., Hjerkinn, B., Hegstad, S., Gossop, M., . . . Waal, H. (2009). Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. *British Journal of Psychiatry, 194*(6), 541-546.

Larance, B., Degenhardt, L., Lintzeris, N., Bell, J., Winstock, A., Dietze, P., . . . Horyniak, D. (2011). Post-marketing surveillance of buprenorphine-naloxone in Australia: Diversion, injection and adherence with supervised dosing. *Drug and Alcohol Dependence, 118*(2-3), 265-273.

Lee, M. C., Wagner, H. N., Tanada, S., Frost, J. J., Bice, A. N., & Dannals, R. F. (1988). Duration of occupancy of opiate receptors by naltrexone. *Journal of Nuclear Medicine, 29*(7), 1207-1211.

Lenne, M. G., Dietze, P., Rumbold, G. R., Redman, J. R., & Triggs, T. J. (2003). The effects of the opioid pharmacotherapies methadone, LAAM and buprenorphine, alone and in combination with alcohol, on simulated driving. *Drug and Alcohol Dependence, 72*(3), 271-278.

Lerner, A. G., Gelkopf, M., Oyffe, I., & Sigal, M. (1995). Home-based inpatient treatment vs. outpatient day clinic treatment: a preliminary report in opiate-dependent patients. *Journal of Nervous and Mental Disease, 183*(11), 715.

Leung, S. Y. (2011). Benzodiazepines, opioids and driving: an overview of the experimental research. *Drug & Alcohol Review, 30*(3), 281-286.

Levy, S., Vaughan, B. L., Angulo, M., & Knight, J. R. (2007). Buprenorphine replacement therapy for adolescents with opioid dependence: Early experience from a children's hospital-based outpatient treatment program. *Journal of Adolescent Health, 40*(5), 477-482.

Ling, W., Charuvastra, C., Collins, J. F., Batki, S., Brown, L. S., Kintaudi, P., . . . Segal, D. (1998). Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction, 93*(4), 475-486.

Ling, W., Farabee, D., Liepa, D., & Wu, L.-T. (2012). The Treatment Effectiveness Assessment (TEA): an efficient, patient-centered instrument for evaluating progress in recovery from addiction. *Substance Abuse and Rehabilitation, 3*, 129-136.

Lingford-Hughes, A., & Nutt, D. (2003). Neurobiology of addiction and implications for treatment. *British Journal of Psychiatry, 182*, 97-100.

Lingford-Hughes, A. R., Welch, S., Peters, L., & Nutt, D. J. (2012). BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. *Journal of Psychopharmacology, 26*(7), 899-952.

Lintzeris, N., Leung, S. Y., Dunlop, A. J., Larance, B., White, N., Rivas, G. R., . . . Ali, R. (2013). A randomised controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence. *Drug and Alcohol Dependence, (in press)*.

Lofwall, M. R., Stitzer, M. L., Bigelow, G. E., & Strain, E. C. (2005). Comparative safety and side effect profiles of buprenorphine and methadone in the outpatient treatment of opioid dependence. *Addictive Disorders & Their Treatment, 4*(2), 49-64.

MacArthur, G. J., Minozzi, S., Martin, N., Vickerman, P., Deren, S., Bruneau, J., . . . Hickman, M. (2012). Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. *BMJ, 345*, e5945.

Madlung-Kratzer, E., Spitzer, B., Brosch, R., Dunkel, D., & Haring, C. (2009). A double-blind, randomized, parallel group study to compare the efficacy, safety and tolerability of slow-release oral morphine versus methadone in opioid-dependent in-patients willing to undergo detoxification. *Addiction, 104*, 1549-1557.

R References

Magura, S., & Rosenblum, A. (2001). Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored. *Mount Sinai Journal of Medicine, 68*(1), 62-74.

Malta, M., Strathdee, S. A., Magnanini, M. M., & Bastos, F. I. (2008). Adherence to antiretroviral therapy for human immunodeficiency virus/acquired immune deficiency syndrome among drug users: a systematic review. *Addiction, 103*, 1242-1257.

Martell, B. A., Arnsten, J. H., Ray, B., & Gourevitch, M. N. (2003). The impact of methadone induction on cardiac conduction in opiate users. *Annals of Internal Medicine, 139*(2), 154-155.

Martin, J. A., Campbell, A., Killip, T., Kotz, M., Krantz, M. J., Kreek, M. J., . . . Administration, S. A. a. M. H. S. (2011). QT interval screening in methadone maintenance treatment: report of a SAMHSA expert panel. *Journal of Addictive Diseases, 30*(4), 283-306.

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews*(3), CD002209. doi: 10.1002/14651858.CD002209.pub2

Mattick, R. P., Kimber, J., Breen, C., & Davoli, M. (2008). Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Systematic Reviews*(2), CD002207. doi: 10.1002/14651858.CD002207.pub3

Mayes, L. C., & Bornstein, M. H. (1996). The context of development for young children from cocaine-abusing families. In P. M. Kato & T. Mann (Eds.), *Handbook of Diversity Issues in Health Psychology* (pp. 69-95). New York, USA: Springer.

McCambridge, J., & Strang, J. (2004). The efficacy of single-session motivational interviewing in reducing drug consumption and perceptions of drug-related risk and harm among young people: results from a multi-site cluster random,ized trial. *Addiction, 99*(1), 39-52.

McDonald, S. D., Vermeulen, M. J., & Ray, J. G. (2007). Risk of fetal death associated with maternal drug dependence and placental abruption: a population-based study. *Journal of Obstetrics and Gynaecology Canada, 29*(7), 556-559.

McLellan, A. T., Lewis, D. C., O'Brien, C. P., & Kleber, H. D. (2000). Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *Journal of the American Medical Association, 284*(13), 1689-1695.

Mello, N. K., & Mendelson, J. H. (1980). Buprenorphine suppresses heroin use by heroin addicts. *Science, 207*(4431), 657-659.

Mendelson, J., & Jones, R. T. (2003). Clinical and pharmacological evaluation of buprenorphine and naloxone combinations: Why the 4:1 ratio for treatment? *Drug and Alcohol Dependence, 70*(Suppl), S29-S37.

Merlo, L. J., Greene, W. M., & Pomm, R. (2011). Mandatory naltrexone treatment prevents relapse among opiate-dependent anesthesiologists returning to practice. *Journal of Addiction Medicine, 5*(4), 279-283.

Miller, W. R., & Rollnick, S. (1991). *Motivational interviewing: Preparing people to change addictive behavior*. New York: The Guilford Press.

Mills, K. L., Lynskey, M., Teesson, M., Ross, J., & Darke, S. (2005). Post-traumatic stress disorder among people with heroin dependence in the Australian treatment outcome study (ATOS): prevalence and correlates. *Drug and Alcohol Dependence, 77*(3), 243-249.

Minozzi, S., Amato, L., Vecchi, S., Davoli, M., Kirchmayer, U., & Verster, A. (2011). Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database of Systematic Reviews*(4). doi: 10.1002/14651858.CD001333.pub4

Mintzer, M. Z., Correia, C. J., & Strain, E. C. (2004). A dose-effect study of repeated administration of buprenorphine/naloxone on performance in opioid-dependent volunteers. *Drug and Alcohol Dependence, 74*, 205-209.

Mitchell, S. G., Gryczynski, J., Schwartz, R. P., O'Grady, K. E., Olsen, Y. K., & Jaffe, J. H. (2013). A randomized trial of intensive outpatient (IOP) vs. standard outpatient (OP) buprenorphine treatment for African Americans. *Drug and Alcohol Dependence, 128*(3), 222-229.

Montoya, I. D., Gorelick, D. A., Preston, K. L., Schroeder, J. R., Umbricht, A., Cheskin, L. J., . . . Fudala, P. J. (2004). Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. *Clinical Pharmacology and Therapeutics, 75*(1), 34-38.

R References

Moody, D. E., Fang, W. B., Morrison, J., & McCance-Katz, E. (2011). Gender differences in pharmacokinetics of maintenance dosed buprenorphine. *Drug and Alcohol Dependence, 118*, 479-483.

Moore, S. K., Marsch, L. A., Badger, G. J., Solhkah, R., & Hofstein, Y. (2011). Improvement in psychopathology among opioid-dependent adolescents during behavioral-pharmacological treatment. *Journal of Addiction Medicine, 5*(4), 264-271.

Moreno, A., Perez-Elias, M. J., Casado, J. L., Munoz, V., Antela, A., Dronda, F., . . . Moreno, S. (2001). Long-term outcomes of protease inhibitor-based therapy in antiretroviral treatment-naive HIV-infected injection drug users on methadone maintenance programmes. *AIDS, 15*(8), 1068-1070.

Moss, A. J. (2006). QTc prolongation and sudden cardiac death: The association is in the detail. *Journal of the American College of Cardiology, 47*(2), 368-369.

Mudric, T. D., Strain, E. C., Stitzer, M. L., & Bigelow, G. E. (1998). Gradual buprenorphine detoxification in an outpatient clinic. *NIDA Research Monograph, 179*, 228.

Mysels, D. J., Cheng, W. Y., Nunes, E. V., & Sullivan, M. A. (2011). The association between naltrexone treatment and symptoms of depression in opioid-dependent patients. *American Journal of Drug and Alcohol Abuse, 37*(1), 22-26.

National Treatment Agency for Substance Misuse. (2002). Models of care for the treatment of drug misusers. Part 2: Full reference report. London, UK: Department of Health. Retrieved from www.nta.nhs.uk

National Treatment Agency for Substance Misuse. (2006). Models of care for treatment of adult drug misusers: Update 2006. London, UK: Department of Health.

Nosyk, B., Sun, H., Evans, E., Marsh, D. C., Anglin, M. D., Hser, Y.-I., & Anis, A. H. (2012). Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: Results from a population-based retrospective cohort study. *Addiction, 107*, 1621-1629.

Nunes, E. V., & Levin, F. R. (2004). Treatment of depression in patients with alcohol or other drug dependence: A meta-analysis. *Journal of the American Medical Association, 291*(15), 1887-1896.

Oliver, P., Keen, J., Rowse, G., Ewins, E., Griffiths, L., & Mathers, N. (2010). The effect of time spent in treatment and dropout status on rates of convictions, cautions and imprisonment over 5 years in a primary care-led methadone maintenance service. *Addiction, 105*(4), 732-739.

Osborn, D. A., Jeffery, H. E., & Cole, M. J. (2010a). Opiate treatment for opiate withdrawal in newborn infants. *Cochrane Database of Systematic Reviews*(10). doi: 10.1002/14651858.CD002059.pub3

Osborn, D. A., Jeffery, H. E., & Cole, M. J. (2010b). Sedatives for opiate withdrawal in newborn infants. *Cochrane Database of Systematic Reviews*(10). doi: 10.1002/14651858.CD002053.pub3

Palmiere, C., Staub, C., La, H. R., & Mangin, P. (2010). Parental substance abuse and accidental death in children. *Journal of Forensic Sciences, 55*(3), 819-821.

Pani, P. P., Vacca, R., Trogu, E., Amato, L., & Davoli, M. (2010). Pharmacological treatment for depression during opioid agonist treatment for opioid dependence. *Cochrane Database of Systematic Reviews*(9). doi: 10.1002/14651858.CD008373.pub2

Papworth, D. P. (1983). High dose buprenorphine for postoperative analgesia. *Anaesthesia, 38*(2), 163.

Peles, E., Schreiber, S., & Adelson, M. (2009). Documented poor sleep among methadone-maintained patients is associated with chronic pain and benzodiazepine abuse, but not with methadone dose. *European Neuropsychopharmacology, 19*(8), 581-588.

Peles, E., Schreiber, S., Bloch, M., Dollberg, S., & Adelson, M. (2012). Duration of methadone maintenance treatment during pregnancy and pregnancy outcome parameters in women with opiate addiction. *Journal of Addiction Medicine, 6*(1), 18-23.

Perez de los Cobos, J., Martin, S., Etcheberrigaray, A., Trujols, J., Batlle, F., Tejero, A., . . . Casas, M. (2000). A controlled trial of daily versus thrice-weekly buprenorphine administration for the treatment of opioid dependence. *Drug and Alcohol Dependence, 59*(3), 223-233.

R References

Petry, N. M., Bickel, W. K., & Badger, G. J. (1999). A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. *Clinical Pharmacology and Therapeutics, 66*(3), 306-314.

Petry, N. M., Bickel, W. K., & Badger, G. J. (2000). A comparison of four buprenorphine dosing regimens using open-dosing procedures: is twice-weekly dosing possible? *Addiction, 95*(7), 1069-1077.

Prendergast, M. L., Messina, N. P., Hall, E. A., & Warda, U. S. (2011). The relative effectiveness of women-only and mixed-gender treatment for substance-abusing women. *Journal of Substance Abuse Treatment, 40*, 336-348.

Prochaska, J. J., Delucchi, K., & Hall, S. M. (2004). A meta-analysis of smoking cessation interventions with individuals in substance abuse treatment or recovery. *Journal of Consulting and Clinical Psychology, 72*(6), 1144-1156.

Prochaska, J. O., DiClemente, C. C., & Norcross, J. C. (1997). In search of how people change: applications to addictive behaviors. In G. A. Marlatt & G. R. VandenBos (Eds.), *Addictive Behaviors: Readings on etiology, prevention and treatment* (pp. 671-696). Washington DC: American Psychological Association.

Quigley, A. J., Bredemeyer, D. E., & Seow, S. S. (1984). A case of buprenorphine abuse. *Medical Journal of Australia, 140*(7), 425-426.

Rapeli, P., Fabritius, C., Alho, H., Salaspuro, M., Wahlbeck, K., & Kalska, H. (2007). Methadone vs. buprenorphine/naloxone during early opioid substitution treatment: A naturalistic comparison of cognitive performance relative to healthy controls. *BMC Clinical Pharmacology, 7*, 5.

Rapeli, P., Fabritius, C., Kalska, H., & Alho, H. (2011). Cognitive functioning in opioid-dependent patients treated with buprenorphine, methadone, and other psychoactive medications: stability and correlates. *BMC Clinical Pharmacology, 11*, 13.

Reid, M. S., Fallon, B., Sonne, S., Flammino, F., Nunes, E. V., Jiang, H., . . . Rotrosen, J. (2008). Smoking cessation treatment in community-based substance abuse rehabilitation programs. *Journal of Substance Abuse Treatment, 35*, 68-77.

Resnick, R. B., Galanter, M., Pycha, C., Cohen, A., Grandison, P., & Flood, N. (1992). Buprenorphine: an alternative to methadone for heroin dependence treatment. *Psychopharmacology Bulletin, 28*(1), 109-113.

Rhoades, H. M., Creson, D., Elk, R., Schmitz, J., & Grabowski, J. (1998). Retention, HIV risk, and illicit drug use during treatment: Methadone dose and visit frequency. *American Journal of Public Health, 88*(1), 34-39.

Robertson, J. R., Raab, G. M., Bruce, M., McKenzie, J. S., Storkey, H. R., & Salter, A. (2006). Addressing the efficacy of dihydrocodeine versus methadone as an alternative maintenance treatment for opiate dependence: A randomized controlled trial. *Addiction, 101*(12), 1752-1759.

Roozen, H. G., Boulogne, J. J., van Tulder, M. W., van den Brink, W., De Jong, C. A., & Kerkhof, A. J. (2004). A systematic review of the effectiveness of the community reinforcement approach in alcohol, cocaine and opioid addiction. *Drug and Alcohol Dependence, 74*(1), 1-13.

Rosado, J., Walsh, S. L., Bigelow, G. E., & Strain, E. C. (2007). Sublingual buprenorphine/naloxone precipitated withdrawal in subjects maintained on 100mg of daily methadone. *Drug and Alcohol Dependence, 90*(2-3), 261-269.

Rosen, M., & Kosten, T. R. (1995). Detoxification and induction onto naltrexone. In A. Cowan & J. W. Lewis (Eds.), *Buprenorphine: Combatting drug abuse with a unique opioid* (pp. 289-305). New York: Wiley-Liss.

Rosen, T. S., & Johnson, H. L. (1982). Children of methadone-maintained mothers: Follow-up to 18 months of age. *Journal of Pediatrics, 101*(2), 192-196.

Rosner, S., Hackl-Herrwerth, A., Leucht, S., Vecchi, S., Srisurapanont, M., & Soyka, M. (2010). Opioid antagonists for alcohol dependence. *Cochrane Database of Systematic Reviews, 8*. doi: 10.1002/14651858.CD001867.pub3

R References

Roux, P., Carrieri, M. P., Cohen, J., Ravaux, I., Poizot-Martin, I., Dellamonica, P., & Spire, B. (2009). Retention in opioid substitution treatment: A major predictor of long-term virological success for HIV-infected injection drug users receiving antiretroviral treatment. *Clinical Infectious Diseases, 49*(9), 1433-1440.

Roy, A. K., McCarthy, C., Kiernan, G., McGorrian, C., Keenan, E., Mahon, N. G., & Sweeney, B. (2012). Increased incidence of QT interval prolongation in a population receiving lower doses of methadone maintenance therapy. *Addiction, 107*(6), 1132-1139.

Ruetsch, C., Tkacz, J., McPherson, T. L., & Cacciola, J. (2012). The effect of telephonic patient support on treatment for opioid dependence: Outcomes at one year follow-up. *Addictive Behaviors, 37*(5), 686-689.

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.

Saxon, A. J., Ling, W., Hillhouse, M., Thomas, C., Hasson, A., Ang, A., . . . Jacobs, P. (2013). Buprenorphine/Naloxone and methadone effects on laboratory indices of liver health: A randomized trial. *Drug and Alcohol Dependence, 128*(1-2), 71-76.

Schisler, R. E., Groninger, H., & Rosielle, D. A. (2012). Counseling patients on side effects and driving when starting opioids #248. *Journal of Palliative Medicine, 15*(4), 484-485.

Schottenfeld, R. S., Pakes, J., O'Connor, P., Chawarski, M., Oliveto, A., & Kosten, T. R. (2000). Thrice-weekly versus daily buprenorphine maintenance. *Biological Psychiatry, 47*(12), 1072-1079.

Schottenfeld, R. S., Pakes, J., Ziedonis, D., & Kosten, T. R. (1993). Buprenorphine: dose-related effects on cocaine and opioid use in cocaine-abusing opioid-dependent humans. *Biological Psychiatry, 34*(1-2), 66-74.

Schottenfeld, R. S., Pakes, J. R., Oliveto, A., Ziedonis, D., & Kosten, T. R. (1997). Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Archives of General Psychiatry, 54*(8), 713-720.

Schwartz, R. P., Kelly, S. M., O'Grady, K. E., Gandhi, D., & Jaffe, J. J. (2012). Randomized trial of standard methadone treatment compared to initiating methadone without counseling: 12-month findings. *Addiction, 107*, 943-952.

Scott, J., Gilvarry, E., & Farrell, M. (1998). Managing anxiety and depression in alcohol and drug dependence. *Addictive Behaviors, 23*(6), 919-931.

Sees, K. L., Delucchi, K. L., Masson, C., Rosen, A., Clark, H. W., Robillard, H., . . . Hall, S. M. (2000). Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: A randomized controlled trial. *Journal of the American Medical Association, 283*(10), 1303-1310.

Sekar, M., & Mimpriss, T. J. (1987). Buprenorphine, benzodiazepines and prolonged respiratory depression. *Anaesthesia, 42*(5), 567-568.

Seligman, N. S., Almario, C. V., Hayes, E. J., Dysart, K. C., Berghella, V., & Baxter, J. K. (2010). Relationship between maternal methadone dose at delivery and neonatal abstinence syndrome. *Journal of Pediatrics, 157*(3), 428-433.

Seow, S. S., Quigley, A. J., Ilett, K. F., Dusci, L. J., Swensen, G., Harrison-Stewart, A., & Rappeport, L. (1986). Buprenorphine: A new maintenance opiate? *Medical Journal of Australia, 144*(8), 407-411.

Shand, F., Gates, J., Fawcett, J., & Mattick, R. (2003). *The treatment of alcohol problems. A review of the evidence*. Canberra: Commonwealth of Australia.

Shmygalev, S., Damm, M., Weckbecker, K., Berghaus, G., Petzke, F., & Sabatowski, R. (2011). The impact of long-term maintenance treatment with buprenorphiine on complex psychomotor and cognitive function. *Drug and Alcohol Dependence, 117*, 190-197.

Sigmon, S. C., Bisaga, A., Nunes, E. V., O'Connor, P. C., Kosten, T., & Woody, G. (2012). Opioid detoxification and naltrexone induction strategies: Recommendations for clinical practice. *American Journal of Drug and Alcohol Abuse, 38*(3), 187-199.

Simon, D. L. (1997). Rapid opioid detoxification using opioid antagonists: history, theory and the state of the art. *Journal of Addictive Diseases, 16*(1), 103-122.

R References

Simpson, D. D., Joe, G. W., Greener, J. M., & Rowan-Szal, G. A. (2000). Modeling year 1 outcomes with treatment process and post-treatment social influences. *Substance Use and Misuse, 35*(12-14), 1911-1930.

Smith, D. K., Johnson, A. B., Pears, K. C., Fisher, P. A., & DeGarmo, D. S. (2007). Child maltreatment and foster care: unpacking the effects of prenatal and postnatal parental substance use. *Child Maltreatment, 12*(2), 150-160.

Smyth, B. P., Fagan, J., & Kernan, K. (2012). Outcome of heroin-dependent adolescents presenting for opiate substitution treatment. *Journal of Substance Abuse Treatment, 42*(1), 35-44.

Soyka, M., Hock, B., Kagerer, S., Lehnert, R., Limmer, C., & Kuefner, H. (2005). Less impairment on one portion of a driving-relevant psychomotor battery in buprenorphine-maintained than in methadone-maintained patients: results of a randomized clinical trial. *Journal of Clinical Psychopharmacology, 25*(5), 490-493.

Soyka, M., Lieb, M., Kagerer, S., Zingg, C., Koller, G., Lehnert, P., . . . Hennig-Fast, K. (2008). Cognitive functioning during methadone and buprenorphine treatment: results of a randomized clinical trial. *Journal of Clinical Psychopharmacology, 28*(6), 699-703.

Spire, B., Lucas, G. M., & Carrieri, M. P. (2007). Adherence to HIV treatment among IDUs and the role of opioid substitution treatment (OST). *International Journal of Drug Policy, 18*, 262-270.

Spooner, C. (1999). Causes and correlates of adolescent drug abuse and implications for treatment. *Drug and Alcohol Review, 18*(4), 453-475.

Staedt, J., Wassmuth, F., Stoppe, G., Hajak, G., Rodenbeck, A., Poser, W., & Ruther, E. (1996). Effects of chronic treatment with methadone and naltrexone on sleep in addicts. *European Archives of Psychiatry and Clinical Neuroscience, 246*(6), 305-309.

Stallvik, M., Nordstrand, B., Kristensen, Ø., Bathen, J., Skogvoll, E., & Spigset, O. (2013). Corrected QT interval during treatment with methadone and buprenorphine - Relation to doses and serum concentrations. *Drug and Alcohol Dependence, 129*(1-2), 88-93.

Stallwitz, A., & Stover, H. (2007). The impact of substitution treatment in prisons - a literature review. *International Journal of Drug Policy, 18*, 464-474.

Stein, M. R., Soloway, I. J., Jefferson, K. S., Roose, R. J., Arnsten, J. H., & Litwin, A. H. (2012). Concurrent group treatment for hepatitis C: Implementation and outcomes in a methadone maintenance treatment program. *Journal of Substance Abuse Treatment, 43*(4), 424-432.

Stewart, S. H., Pihl, R. O., Conrod, P. J., & Dongier, M. (1998). Functional associations among trauma, PTSD, and substance-related disorders. *Addictive Behaviors, 23*(6), 797-812.

Stimson, G. V. (1995). AIDS and injecting drug use in the United Kingdom, 1987-1993: the policy response and the prevention of the epidemic. *Social Science and Medicine, 41*(5), 699-716.

Strain, E. C., Moody, D. E., Stoller, K. B., Walsh, S. L., & Bigelow, G. E. (2004). Relative bioavailability of different buprenorphine formulations under chronic dosing conditions. *Drug and Alcohol Dependence, 74*(1), 37-43.

Strand, M. C., Fjeld, B., Arnestad, M., & Mørland, J. (2013). Can patients receiving opioid maintenance therapy safely drive? A systematic review of epidemiological and experimental studies on driving ability with a focus on concomitant methadone or buprenorphinie administration. *Traffic Injury Prevention, 14*, 26-38.

Straus, S. M. J. M., Kors, J. A., De Bruin, M. L., van der Hooft, C. S., Hofman, A., Heeringa, J., . . . Witteman, J. C. M. (2006). Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *Journal of the American College of Cardiology, 47*(2), 362-367.

Street, K., Harrington, J., Chiang, W., Cairns, P., & Ellis, M. (2004). How great is the risk of abuse in infants born to drug-using mothers? *Child: Care, Health and Development, 30*(4), 325-330.

R References

Stubbs, M., Hides, L., Howard, J., & Arcuri, A. (2004). Psychostimulants and young people. In A. Baker, N. K. Lee & L. Jenner (Eds.), *Models of intervention and care for psychostimulant users* (pp. 133-153). Canberra: Commonwealth of Australia.

Sullivan, L. E., & Fiellin, D. A. (2004). Hepatitis C and HIV infections: implications for clinical care in injection drug users. *American Journal on Addictions, 13*, 1-20.

Swindle, R. W., Peterson, K. A., Paradise, M. J., & Moos, R. H. (1995). Measuring substance abuse program treatment orientations: The Drug and Alcohol Program Treatment Inventory. *Journal of Substance Abuse, 7*, 61-78.

Teesson, M., Havard, A., Ross, J., & Darke, S. (2006). Outcomes after detoxification for heroin dependence: findings from the Australian Treatment Outcome Study (ATOS). *Drug & Alcohol Review, 25*(3), 241-247.

Teesson, M., Mills, K., Ross, J., Darke, S., Williamson, A., & Havard, A. (2008). The impact of treatment on 3 years' outcome for heroin dependence: findings from the Australian Treatment Outcome Study (ATOS). *Addiction, 103*(1), 80-88.

Teesson, M., Ross, J., Darke, S., Lynskey, M., Ali, R., Ritter, A., & Cooke, R. (2006). One year outcomes for heroin dependence: Findings from the Australian Treatment Outcome Study (ATOS). *Drug and Alcohol Dependence, 83*(2), 174-180.

Teichtahl, H., Prodromidis, A., Miller, B., Cherry, G., & Kronborg, I. (2001). Sleep-disordered breathing in stable methadone programme patients: a pilot study. *Addiction, 96*(3), 395-403.

Thorn, S. E., Rawal, N., & Wennhager, M. (1988). Prolonged respiratory depression caused by sublingual buprenorphine. *Lancet, 1*(8578), 179-180.

Tiffany, S. T., Carter, B. L., & Singleton, E. G. (2000). Challenges in the manipulation, assessment and interpretation of craving relevant variables. *Addiction, 95*(Suppl 2), S177-S187.

Tucker, T., Ritter, A., Maher, C., & Jackson, H. (2004). Naltrexone maintenance for heroin dependence: uptake, attrition and retention. *Drug & Alcohol Review, 23*(3), 299-309.

Tucker, T. K., & Ritter, A. J. (2000). Naltrexone in the treatment of heroin dependence: a literature review. *Drug and Alcohol Review, 19*(1), 73-82.

Umbricht, A., Montoya, I. D., Hoover, D. R., Demuth, K. L., Chiang, C. T., & Preston, K. L. (1999). Naltrexone shortened opioid detoxification with buprenorphine. *Drug and Alcohol Dependence, 56*(3), 181-190.

UNAIDS. (2010). Global report: UNAIDS report on the global AIDS epidemic. *Joint United Nations Programme on HIV/AIDS*. Retrieved from www.unaids.org

UNODC. (2003). Drug abuse treatment and rehabilitation: A practical planning and implementation guide. Vienna: United Nations Office on Drugs and Crime.

Velez, M. L., Jansson, L. M., Montoya, I. D., Schweitzer, W., Golden, A., & Svikis, D. (2004). Parenting knowledge among substance abusing women in treatment. *Journal of Substance Abuse Treatment, 27*(3), 215-222.

Wachman, E. M., Newby, P. K., Vreeland, J., Byun, J., Bonganzi, A., Bauchner, H., & Philipp, B. L. (2011). The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence syndrome. *Journal of Addiction Medicine, 5*(4), 293-299.

Walsh, S. L., Preston, K. L., Bigelow, G. E., & Stitzer, M. L. (1995). Acute administration of buprenorphine in humans: partial agonist and blockade effects. *Journal of Pharmacology and Experimental Therapeutics, 274*(1), 361-372.

Walsh, S. L., Preston, K. L., Stitzer, M. L., Cone, E. J., & Bigelow, G. E. (1994). Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clinical Pharmacology and Therapeutics, 55*(5), 569-580.

Ward, J., Mattick, R. P., & Hall, W. (1998). How long is long enough? Answers to questions about the duration of methadone maintenance treatment. In J. Ward, R. P. Mattick & W. Hall (Eds.), *Methadone Maintenance Treatment and Other Opioid Replacement Therapies* (pp. 305-336). Amsterdam: Harwood Academic Publishers.

R References

Washton, A. M., Pottash, A. C., & Gold, M. S. (1984). Naltrexone in addicted business executives and physicians. *Journal of Clinical Psychiatry, 45*(9), 39-41.

Weiss, R. D., Griffin, M. L., Najavits, L. M., Hufford, C., Kogan, J., Thompson, H. J., . . . Siqueland, L. (1996). Self-help activities in cocaine dependent patients entering treatment: results from NIDA collaborative cocaine treatment study. *Drug and Alcohol Dependence, 43*(1-2), 79-86.

Welle-Strand, G. K., Skurtveit, S., Jones, H. E., Waal, H., Bakstad, B., Bjarko, L., & Ravndal, E. (2013). Neonatal outcomes following in utero exposure to methadone or buprenorphine: A national cohort study of opioid-agonist treatment of pregnant women in Norway from 1996 to 2009. *Drug and Alcohol Dependence, 127*(1-3), 200-206.

WHO. (2009). Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva, Switzerland: World Health Organization, Department of Mental Health and Substance Abuse.

Williams, H. (2002). Dual Diagnosis - an overview: Fact or fiction? In G. H. Rassool (Ed.), *Dual Diagnosis: Substance Misuse and Psychiatric Disorders* (pp. 3-11). Oxford: Blackwell Science.

Winstock, A. R., Lintzeris, N., & Lea, T. (2011). “Should I stay or should I go?” Coming off methadone and buprenorphine treatment. *International Journal of Drug Policy, 22*(1), 77-81.

Witkiewitz, K., Bowen, S., Douglas, H., & Hsu, S. H. (2013). Mindfulness-based relapse prevention for substance craving. *Addictive Behaviors, 38*(2), 1563-1571.

Woody, G. E., Poole, S. A., Subramaniam, G., Dugosh, K., Bogenschutz, M., Abbott, P., . . . Fudala, P. (2008). Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: A randomized trial. *JAMA, 300*(17), 2003-2011.

Yancovitz, S. R., Des Jarlais, D. C., Peyser, N. P., Drew, E., Friedmann, P., Trigg, H. L., & Robinson, J. W. (1991). A randomized trial of an interim methadone maintenance clinic. *American Journal of Public Health, 81*(9), 1185-1191.

Zanis, D. A., & Woody, G. E. (1998). One-year mortality rates following methadone treatment discharge. *Drug and Alcohol Dependence, 52*, 257-260.

Zutler, M., & Holty, J. E. (2011). Opioids, sleep, and sleep-disordered breathing. *Current Pharmaceutical Design, 17*(15), 1443-1449.

Glossary of Terms and Abbreviations

Abstinence	Not using a particular drug; being drug-free
Addiction	A chronic, relapsing disorder characterised by compulsion to seek and take a substance, loss of control over substance use, and a negative emotional state when access to the substance is prevented (Koob & Volkow, 2010).
Adverse event	Any untoward medical occurrence in a patient administered medicine and which does not necessarily have a causal relationship with this medicine.[23]
Adverse reaction	A harmful or undesirable response to an agent/substance.[24]
Affinity	The strength with which a drug binds to its receptor
Agonist	A substance that binds to and activates the matching receptor
Antagonist	A substance that binds to a receptor without activating it; a blocking agent
Aversive agent	Medication that produces an unpleasant reaction, for example disulfiram (Antabuse) is aversive in combination with alcohol.
Buprenorphine	Derived from the opium alkaloid, thebaine; a partial opioid agonist with high affinity for the mu opioid receptor. See 2.1.2
COWS	Clinical Opiate Withdrawal Scale See Appendix 2
Combination preparation	Refers to preparations for sublingual administration containing buprenorphine and naloxone (e.g. Suboxone®)
Compulsivity	Elements of behaviour that result in perseveration in responding in the face of adverse consequences, perseveration in responding in the face of incorrect responses in choice situations, or persistent reinitiation of habitual acts.
Craving	Subjective experience of an urge or desire to use substances (Witkiewitz, et al., 2013) that may be diverse in nature.
Dependence	A state in which drug use has become central to a person's thoughts, emotions and activities; stopping, or reducing the drug suddenly, can lead to physical withdrawal symptoms. See Appendix 1
Detoxification	Management of the signs and symptoms of withdrawal that occur on cessation of a substance on which a person is dependent.

LINK

[23]Therapeutic Goods Information (Database of Adverse Event Notifications) Specification 2012. Available from http://www.comlaw.gov.au/Details/F2012L01337. Accessed 14 March 2013.

G Glossary of Terms and Abbreviations

Dissociation	A measure of the disengagement or uncoupling of a drug from its receptor
Euphoria	Feeling of well-being – the 'high' or 'rush'
Illicit	Not legal
Impulsivity	A predisposition toward rapid, unplanned reactions to internal and external stimuli without regard for the negative consequences of these reactions to themselves or others.
Intrinsic activity	The degree to which a drug activates its receptors
Lapse	Relevant only to abstinence-oriented programs where it is used to indicate an instance of alcohol or other drug use.
Methadone	A synthetic opioid agonist See 2.1.1
Mono preparation	Refers to preparations containing only buprenorphine (e.g. Subutex®)
Naloxone	An antagonist at the mu opioid receptor with a short half-life that is used in the treatment of opioid overdose, but is also combined with buprenorphine to deter misuse and diversion.
Naltrexone	An antagonist at the mu opioid receptor with a long half-life that is administered orally. See 2.1.3
Negative reinforcement	The process by which removal of an adverse stimulus (e.g. negative emotional state of drug withdrawal) increases the probability of a response (e.g. dependence-induced drug intake).
OOWS	Objective Opiate Withdrawal Scale See appendix 2
Opiate	One of a group of alkaloids, including morphine and heroin, derived from the opium poppy (Papaver somniferum) with the ability to induce analgesia, euphoria and, in higher doses, stupor, coma and respiratory depression.
Opioid	All drugs with morphine-like activity, both natural opiates and synthetic drugs such as methadone.
Opioid receptors	Brain structures that mediate the effects of opioid drugs. See also Receptors.

G Glossary of Terms and Abbreviations

QTc interval	That part of a person's electrocardiogram reading that begins at the onset of the QRS complex and extends to the end of the T wave. The QTc interval represents the time between the start of ventricular depolarisation and the end of ventricular repolarisation See Prolongation of QTc interval in 2.3.7.
Positive reinforcement	The process by which presentation of a stimulus, usually pleasant (e.g. the drug itself), increases the probability of a response.
Rapid opioid detox	A general term for procedures involving the use of opioid antagonists to induce withdrawal from opioids See 2.2.3
Receptors	Brain structures which bind particular drugs; the effects of a drug are experienced when the drug has attached itself to its corresponding receptor
Recovery capital	The sum total of all the personal, social, and community resources a person can draw on to begin and sustain his recovery from drug and alcohol problems (Groshkova, et al., 2013)
Relapse	Return to problematic use of alcohol or other drugs.
ShOWS	Short Opiate Withdrawal Scale See Appendix 2
SOWS	Subjective Opiate Withdrawal Scale See Appendix 2
Takeaways	Doses of medication provided for administration away from the dosing point; administration of takeaways may or may not be supervised by a responsible adult. See also unsupervised dosing See 2.3.6.
Tolerance	Requiring higher doses of the drug to experience the same effects
Unsanctioned	Usually referring to use of drugs that is not in accordance with a medical prescription
Unsupervised dosing	Refers to takeaway doses of medication that are administered without supervision by a responsible adult. See also Takeaways. See 2.3.6
Withdrawal	Signs and symptoms associated with cessation of a substance on which a person is dependent.

1 Appendix

Definitions of opioid dependence

Diagnostic and Statistical Manual of Mental Disorders

LINK

See http://www.psych.org/practice/dsm

After a major review, the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has now been released.

DSM-IV had separate diagnoses of substance abuse and dependence which have been combined in DSM-5 into a diagnosis for substance use disorder. The DSM-5 substance use disorder criteria are nearly identical to the DSM-IV substance abuse and dependence criteria combined into a single list, with two exceptions. The DSM-IV recurrent legal problems criterion for substance abuse has been deleted from DSM-5, and a new criterion, craving or a strong desire or urge to use a substance, has been added. In addition, the threshold for substance use disorder diagnosis in DSM-5 is set at two or more criteria, in contrast to a threshold of one or more criteria for a diagnosis of DSM-IV substance abuse and three or more for DSM-IV substance dependence. Severity of the DSM-5 substance use disorders is based on the number of criteria endorsed: 2-3 criteria indicate a mild disorder; 4-5 criteria, a moderate disorder; and 6 or more, a severe disorder. Early remission from a DSM-5 substance use disorder is defined as at least 3 but less than 12 months without substance use disorder criteria (except craving), and sustained remission is defined as at least 12 months without criteria (except craving).

DSM-IV criteria for opioid dependence are:

“A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by three or more of the following occurring at any time in the same 12 month period:

- Tolerance as defined by either of the following:
  - A need for markedly increased amounts of opioids to achieve intoxication or desired effect;
  - Markedly diminished effect with continued use of the same amount of opioids.
- Withdrawal as manifested by either of the following:
  - The characteristic withdrawal syndrome for opioids.
  - Opioids or a closely related substance are taken to relieve or avoid withdrawal symptoms.
- Opioids are often taken in larger amounts or over a longer period than was intended.
- There is a persistent desire or unsuccessful attempts to cut down or control opioid use.
- A great deal of time is spent in activities necessary to obtain opioids, use opioids, or recover from their effects.
- Important social, occupational, or recreational activities are given up or reduced because of opioid use.

1 Definitions of opioid dependence

- The opioid use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.

International Classification of Diseases, 10th edition (ICD-10):

LINK

See www.who.int/classifications/icd/en/

Opioid dependence is defined by the presence of three or more of the following features present simultaneously at any one time in the preceding year:

- a strong desire or sense of compulsion to take opioids;
- difficulties in controlling opioid use;
- a physiological withdrawal state;
- tolerance;
- progressive neglect of alternative pleasures or interests because of opioid use;
- persisting with opioid use despite clear evidence of overtly harmful consequences.

2 Appendix

Assessment of opioid withdrawal

There are various opioid withdrawal scales available to refer to. Subjective scales are far more sensitive to changes in withdrawal severity, and are better predictors of patient outcomes. Objective scales are not only less sensitive, but usually need to be administered by a health professional. They may nevertheless be useful in corroborating subjective ratings, particularly in individuals who are thought to be over- or under-rating their withdrawal severity.

The Subjective and Objective Opiate Withdrawal Scales assess the severity of withdrawal at the time the scale is administered. These scales can be used multiple times in any day. The Short Opiate Withdrawal Scale is often abbreviated in literature to SOWS, but referred to here as ShOWS to avoid confusion with the Subjective Opiate Withdrawal Scale. This scale assesses the patient's experience of withdrawal in the preceding 24 hours. As such the ShOWS is only valid for once daily administration. It includes assessment of sleep disturbance which is an aspect of withdrawal that is significant to patients. The Clinical Opiate Withdrawal Scale (COWS) is the newest of the scales. It combines objective and subjective items. Like the SOWS and OOWS it can be administered multiple times in a day. It has the advantage of being quick to administer.

2 Assessment of opioid withdrawal

Objective Opiate Withdrawal Scale (OOWS)

Observe the patient during a 5 Minute observation period. Then indicate a score for each of the opioid withdrawal signs listed below (items 1-13). Add the scores for each item to obtain the total score

DATE: TIME:

SIGN	MEASURES		SCORE
1 Yawning	0 = no yawns	1 = ≥ 1 yawn	
2 Rhinorrhoea	0 = < 3 sniffs	1 = ≥ 3 sniffs	
3 Piloerection (observe arm)	0 = absent	1 = present	
4 Perspiration	0 = absent	1 = present	
5 Lacrimation	0 = absent	1 = present	
6 Tremor (hands)	0 = absent	1 = present	
7 Mydriasis	0 = absent	1 = ≥ 3 mm	
8 Hot and Cold flushes	0 = absent	1 = shivering / huddling for warmth	
9 Restlessness	0 = absent	1 = frequent shifts of position	
10 Vomiting	0 = absent	1 = present	
11 Muscle twitches	0 = absent	1 = present	
12 Abdominal cramps	0 = absent	1 = Holding stomach	
13 Anxiety	0 = absent	1 = mild - severe	
TOTAL SCORE			

Range 0-13

Ref: Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987) Two new rating scales for opiate withdrawal, American Journal of Alcohol Abuse, 13, 293-308.

2 Assessment of opioid withdrawal

Subjective Opiate Withdrawal Scale (SOWS)

Please score each of the 16 items below according to how you feel now
(Circle one number)

DATE: TIME:

Symptom	Not at all	A little	Moderately	Quite a bit	Extremely
1 I feel anxious	0	1	2	3	4
2 I feel like yawning	0	1	2	3	4
3 I am perspiring	0	1	2	3	4
4 My eyes are teary	0	1	2	3	4
5 My nose is running	0	1	2	3	4
6 I have goosebumps	0	1	2	3	4
7 I am shaking	0	1	2	3	4
8 I have hot flushes	0	1	2	3	4
9 I have cold flushes	0	1	2	3	4
10 My bones and muscles ache	0	1	2	3	4
11 I feel restless	0	1	2	3	4
12 I feel nauseous	0	1	2	3	4
13 I feel like vomiting	0	1	2	3	4
14 My muscles twitch	0	1	2	3	4
15 I have stomach cramps	0	1	2	3	4
16 I feel like using now	0	1	2	3	4

Range 0-64.

Ref: Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987) Two new rating scales for opiate withdrawal, American Journal of Alcohol Abuse, 13, 293-308.

2 Assessment of opioid withdrawal

The Short Opiate Withdrawal Scale (ShOWS)

Please put a check mark in the appropriate box if you have suffered from any of the following conditions in the last 24 hours:

DATE: TIME:

Symptom	None	Mild	Moderate	Severe
Feeling Sick				
Stomach Cramps				
Muscle Spasms/Twitching				
Feelings of Coldness				
Heart Pounding				
Muscular Tension				
Aches and Pains				
Yawning				
Runny Eyes				
Insomnia/Problems Sleeping				

Scoring: None = 0, Mild = 1, Moderate = 2, Severe = 3

Ref: Gossop, M. (1990) The development of a short opiate withdrawal scale (SOWS). Addictive Behaviors 15, 487-490.

2 Assessment of opioid withdrawal

Clinical Opiate Withdrawal Scale (COWS)

For each item, write in the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

DATE: TIME:

Resting Pulse Rate: (record beats per minute) *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120				
Sweating: *Over past ½ hour not accounted for by room temperature or patient activity* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face				
Restlessness: *Observation during assessment temperature or patient activity* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds				
Pupil size: 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible				
Bone or Joint aches: *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort				

(Continued)

2 Assessment of opioid withdrawal

Clinical Opiate Withdrawal Scale (COWS) *(cont)*

Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks				
GI Upset: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhoea 5 Multiple episodes of diarrhoea or vomiting				
Tremor *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching				
Yawning *observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute				
Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult				
Gooseflesh skin 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection				
TOTAL SCORES				

The total score is the sum of all 11 items
Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

Ref: Wesson D.R. & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). Journal of Psychoactive Drugs 35(2):253-259.

2 Assessment of opioid withdrawal

Modified Finnegan Scale for Neonates

This scale[20] is used for the measurement of neonatal abstinence syndrome due to neonatal opioid withdrawal. Infants of mothers known or suspected to be drug users who are showing signs of withdrawal should be scored every four hours. The scoring should be applied in a consistent manner by personnel who are experienced in dealing with such infants. Caution must be exercised before symptoms listed here are accepted as part of drug withdrawal. For example, symptoms such as fever, tachypnoea or seizures could be due to sepsis, which should be excluded first with appropriate tests.

System	Signs and symptoms	Score
Central Nervous System Disturbances	High-pitched cry	2
	Continuous high-pitched cry	3
	Sleeps <1 hour after feeding	3
	Sleeps <2 hours after feeding	2
	Sleeps <3 hours after feeding	1
	Mild tremors disturbed	1
	Moderate-severe tremors disturbed	2
	Mild tremors undisturbed	3
	Moderate-severe tremors undisturbed	4
	Increased muscle tone	2
	Excoriation (specify area)	1
	Myoclonic jerks	3
	Generalised convulsions	5
Metabolic/Vasomotor/ Respiratory Disturbances	Fever (37.3-38.3 deg C)	1
	Fever (>38.3 deg C)	2
	Frequent yawning (>3-4 times)	1
	Nasal snuffiness	1
	Sneezing (>3-4 times)	1
	Nasal flaring	2
	Respiratory rate > 60/min	1
	Respiratory rate > 60/min + retractions	2
Gastrointestinal disturbances	Excessive sucking	1
	Poor feeding	2
	Regurgitation	2
	Projectile vomiting	3
	Loose stools	2
	Watery stools	3

[20] There are several versions of this scale. This is the Royal Prince Alfred Hospital version.

Infants scored three consecutive abstinence scores averaging more than 8 (e.g. 9-7-9) or ≥12 for two scores require treatment. The scoring interval should be four hourly until the infant has been stabilised. (Reference: Finnegan L (1980). Drug Dependence in Pregnancy. London, Castle House Publications.)

3 Appendix

Clinically significant interactions between methadone, buprenorphine and other medications

This appendix lists some prescription medications that are known to, or may potentially result in clinically significant interactions when used in combination with methadone or buprenorphine. The list is not exhaustive; if in doubt, specialist advice should be sought.

The listing draws on information from www.opioiddruginteractions.com/.

In the tables ++ indicates a strong clinical interaction, + indicates an interaction of less significance, ? indicates the potential for interaction with limited supporting evidence. All interactions should be avoided if possible, or patients should be monitored and drug regimens adjusted if necessary.

1. Increased sedative effects

The medications in this group may increase the risk of overdose through additive CNS depression, or increased plasma levels of methadone or buprenorphine resulting from decreased metabolism or decreased urinary clearance.

Clinical significance for:		**Medication**
Methadone	**Buprenorphine**	
++	++	Amitriptyline
	++	Atazanavir
++	++	Benzodiazepines (alprazolam, diazepam, triazolam)
?		Ciproflaxin
++		Citalopram/escitalopram
?		Erythromycin
++	?	Fluconazole
+	?	Fluoxetine
++	+	Fluvoxamine
+	?	Indinavir
?	?	Ketoconazole
+		Moclobemide
?		Omeprazole
?	?	Ritonavir (avoid using in combination with atazanavir)
?		Sertraline
+		Urine alkalisers e.g. sodium bicarbonate
++	+	Zopiclone

3 Clinically significant interactions between methadone, buprenorphine and other medications

2. *Withdrawal symptoms or adverse effects*

The medications in this group may cause decreased plasma levels and withdrawal symptoms due to increased metabolism of methadone or buprenorphine, or may cause adverse effects through other mechanisms.

Clinical significance for:		Medication
Methadone	**Buprenorphine**	
++		Carbamazepine
+	?	Cimetidine
+		Disulfiram (if used in conjunction with methadone formulations containing alcohol)
+	?	Hypericum perforatum (St Johns Wort)
+		Moclobemide (may cause serotonin toxicity)
+		Nevirapine
	?	Nifedipine
++	?	Phenytoin
++	?	Rifampicin
++	++	Rifabutin
+	+	Urine acidifiers e.g. ascorbic acid

3. *Prolongation of QTc interval*

These medications may be contraindicated by the manufacturer for use in combination with methadone or buprenorphine due to their capacity to cause prolongation of the QTc interval.

Clinical significance for:		Medication
Methadone	**Buprenorphine**	
+	+	Domperidone
+		Citalopram/escitalopram
?	?	Erythromycin
+	?	Thioridazine

4. *Effects on other medications*

Methadone and buprenorphine may also impact adversely on the other medications that may be used in combination.

Clinical significance for:		Medication
Methadone	**Buprenorphine**	
++		Atazanavir (methadone may decrease serum levels)
++		Desipramine (metabolism decreased leading to increased plasma levels of desipramine)
++		Nifedipine (methadone may inhibit metabolism)
++		Zidovudine (metabolism is decreased leading to increased plasma levels of zidovudine. Symptoms of zidovudine toxitiy can be misinterpreted as opioid withdrawal)

4 Appendix

Management of acute opioid withdrawal precipitated by naltrexone [26]

Introduction

There have been a number of reports of opioid-dependent people self-administering naltrexone, precipitating a severe withdrawal reaction requiring hospital treatment. These guidelines are to assist medical and nursing staff to recognise and manage naltrexone precipitated withdrawal.

Precipitated withdrawal

Onset of naltrexone-precipitated withdrawal occurs 20 to 60 minutes following ingestion.

- Gastrointestinal symptoms are usually predominant.
- Severe vomiting and diarrhoea may occur.
- Patients become agitated and distressed, and delirium with confusion is common.
- Signs of sympathetic overactivity, particularly profuse sweating and piloerection, may occur.
- If a patient has taken sedative drugs in conjunction with naltrexone, as commonly occurs, delirium is exacerbated but other signs may be less clear.

There are significant risks associated with precipitated withdrawal.

- Most deaths associated with precipitated withdrawal appear to have been the result of aspiration associated with high doses of sedative drugs.
- In people who have received high doses of sedating drugs, delayed respiratory depression emerging after acute withdrawal has subsided, may have contributed to deaths.
- Fluid and electrolyte problems secondary to vomiting and diarrhoea.
- During acute delirium, confused patients must be considered at risk and require medical care.

Diagnosis and assessment

History may be difficult to obtain from confused patients, particularly if they are defensive about being identified as heroin users.

- Suspect naltrexone precipitated withdrawal in any patient presenting with signs of opioid withdrawal in conjunction with delirium or intractable vomiting.
- A history of opioid dependence should be gained from the patient, significant others or by inspection of injection sites for recent track marks. (An absence of track marks should not exclude this diagnosis).

[26] These guidelines were developed as part of the National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project. The guidelines were written by Malcolm Young, Langton Centre, Sydney.

4 Management of acute opioid withdrawal precipitated by naltrexone [26]

Careful assessment of the degree of sedation, and of the patient's capacity to protect their airway, is essential.

- The use of flumazenil to reverse sedation is not recommended due to the chance of the presenting patient having concurrent benzodiazepine dependence and the risk of inducing life-threatening seizures.
- Deeply sedated, vomiting patients may require intubation and ICU management.
- It may be desirable to check electrolytes and arterial blood gases.

Management

Naltrexone precipitated withdrawal is self-limiting, with delirium usually lasting only about 4 hours. Treatment is supportive and symptomatic.

Patients with vomiting may require fluid and electrolyte replacement.

- Although most patients will experience fluid loss to some degree, the insertion of i.v. cannulae and administration of fluids should be balanced against potential problems. Patients in delirium frequently remove i.v. lines.
- Most patients will be capable of tolerating oral fluids within 12 hours of ingestion of naltrexone.

During naltrexone-induced withdrawal delirium, most patients can be reoriented. This is critical in both obtaining a history and in managing the confused patient.

The most important part of management is reassuring the patient that symptoms, although severe, will be short lived.

Treating staff should be aware that the antagonist induced withdrawal syndrome is extremely traumatic and that patients expressing fear of death, for example, should not be treated contemptuously, but given appropriate, repeated reassurance.

The administration of opioid agonists is unlikely to be helpful. Patients should be warned that taking heroin will not alleviate symptoms.

In managing vomiting and diarrhoea, clinical experience indicates that conventional anti-emetics provide little relief. Octreotide (Sandostatin) 100ug is the drug of choice in reducing vomiting and diarrhoea.

Agitation and sympathetic overactivity can be treated with clonidine (150ug po, or 100ug im, repeated after 2 hours if agitation persists and hypotension is not a problem).

When urgent sedation is imperative (where patients are violent and confused), midazolam 5-10 mg im may be helpful.

When abdominal cramps are a problem, a single dose of 20 mg hyoscine-N-butylbromide (Buscopan) can help.

Additional management

Patients and families should be informed that residual symptoms may persist for up to 7 days. Patients need to be warned of the risk of overdose if they use heroin following naltrexone.

5 Appendix

Withdrawal states from commonly used drugs

Drug class	Onset	Duration	Symptoms
Opioids	8-12 hours (short acting). Delayed for longer acting drugs.	Peaks 2-4 days. Ceases 7-10 days (short acting). Longer for long acting opioids.	Anxiety, muscle tension, muscle and bone ache, muscle cramps, sleep disturbance, sweating, hot and cold flushes, piloerection(goosebumps), yawning, lacrimation, rhinorrhoea, abdominal cramps, nausea, vomiting, diarrhoea, palpitations, elevated blood pressure, elevated pulse, dilated pupils.
Alcohol	As blood alcohol falls, depends on rate of fall and hours after last drink	5-7 days	Anxiety, agitation, sweating, tremor, nausea, vomiting, abdominal cramps, diarrhoea, anorexia, craving, insomnia, elevated blood pressure, elevated pulse, temperature, headache, seizures, confusion, perceptual distortions, disorientation, hallucinations, hyperpyrexia.
Benzodiazepines	1-10 days depending on half-life	3-6 days, longer in some people	Anxiety, insomnia, muscle aching and twitching, perceptual changes, feelings of unreality, depersonalisation, seizures.
Stimulants	8-36 hours	Several days, occasionally 2-3 weeks	Lethargy, depression, irritability, hyperphagia, anhedonia, dysphoria, desire for sleep increased.
Cannabis	Usually days	Weeks	Irritability, anxiety, insomnia, anorexia, sweating, muscle spasms, headaches.

From NSW Methadone Maintenance Treatment Clinical Practice Guidelines.
Used with permission.

6 Appendix

Signs of intoxication with commonly used drugs

Class of drug	Intoxication	Overdose
Opioids (e.g. methadone, heroin, morphine)	Constriction of pupils Itching/scratching Sedation/somnolence Lowered blood pressure Slowed pulse Hypoventilation	Loss of consciousness Respiratory depression Pinpoint pupils Hypotension Bradycardia Pulmonary oedema
Alcohol	Relaxation Disinhibition Impaired coordination Impaired judgement Decreased concentration Slurred speech Ataxia Vomiting	Disorientation/confusion Respiratory depression Loss of consciousness Loss of bladder control
Benzodiazepines (e.g. diazepam, oxazepam, alprazolam, flunitrazepam)	Disinhibition Sedation Drooling Incoordination Slurred speech Lowered blood pressure Dizziness	Stupor/coma Ataxia Confusion Respiratory depression
Stimulants (e.g. amphetamines, cocaine)	Hyperactivity Restlessness Agitation Anxiety/nervousness Great dilation of pupils Elevated blood pressure Increased pulse Raised temperature Sweating Tremor	Panic Acute paranoid psychosis Seizures Cardiac arrhythmias Myocardial ischaemia Hypertensive crisis Cerebrovascular accidents Hyperpyrexia Dehydration
Cannabis	Relaxation Decreased concentration Decreased psychomotor performance Impaired balance Conjunctival inflammation	Paranoid psychosis Confusion Agitation Anxiety/panic Hallucinations

From NSW Methadone Maintenance Treatment Clinical Practice Guidelines.
Used with permission.

7 Appendix

Detection times for selected drugs in urine[27]

Drug	Time*
Alcohol	4-24 hours
Amphetamine-like substances: including amphetamine, methamphetamine, ecstasy (MDMA)	2-4 days
Benzodiazepines – Short acting – Long-acting (high-level misuse)	 1-3 days 1-2 weeks (up to 6 weeks)
Buprenorphine (sublingual)	1-2 weeks
Cannabis (50 µg/L screen cut-off) – Occasional – Chronic, very heavy use	 1-3 weeks 4-6 weeks (may be up to 12 weeks)
Cocaine metabolites	2-4 days
Monoacetylmorphine (heroin metabolite)	12-24 hours
Methadone	3-4 days
Opiates: codeine, morphine	2-3 days (metabolites 3-6 days)
Oxycodone	1-2 days

*Times are estimates only. Detection times for an individual may vary with specific drug, dose and metabolism.

[27] Based on information supplied by SA Pathology, Frome Road, Adelaide.

8 Appendix

Equivalent opioid doses[28]

Note that this table is based on studies of bioequivalence for acute analgesic effects which were largely undertaken in opioid-naïve individuals using low doses of opioid drugs. Consequently the validity of these data in the context of opioid substitution treatment is limited. The table should be used as a guide only and clinical judgement used on a case by case basis depending on the circumstances.

Approximate equivalent doses of opioid analgesics		
	Parenteral (mg)	Oral (mg)
Morphine	10	30
Buprenorphine	0.4	0.8 (SL)
Codeine	130	200
Diamorphine	5	–
Fentanyl	0.15 – 0.2	–
Hydromorphone	2	7.5
Methadone	10	15
Oxycodone	10	20
Pethidine	75	300
Tramadol	100	100

[28] Doyle, D & Woodruff, R (2008). *The IAHPC Manual of Palliative Care*, 2nd Edition. Published by IAHPC Press. Available from http://hospicecare.com/about-iahpc/publications/manuals-guidelines-books/manual-of-palliative-care/pain3/. Accessed 4 April 2013.

9 Appendix

ATOP Quick Reference Guide

(for comprehensive administration instructions refer to the ATOP Manual)

About the ATOP

The Australian Treatment Outcomes Profile (ATOP) is a simple set of questions to improve and simplify the review process and assist with on-going treatment planning and clinical handover. The answers to these questions will also provide data for measuring treatment outcomes.

Introducing the ATOP

- I'd like to spend a few minutes completing a short interview (called the ATOP) with you.
- The questions look at substance use, health risk and wellbeing over the last four weeks - some of them may not be relevant to you.
- We are asking all our clients to complete the ATOP.
- We use the information as part of the way we will plan your care and to evaluate how well the service is providing treatment to clients.
- It's important that you answer as accurately and truthfully as you can, but if you don't want to answer any of the questions say so and I'll move on.
- Once we've completed the ATOP we can look more in-depth at your needs and goals

How to complete the ATOP

1. Carefully explain confidentiality (see box)

Don't assume that clients will be equally concerned or blasé about confidentiality issues.

2. Enter:

Patient Label
(Name, MRN, date of birth and sex);

Your name;

Date of ATOP;

The stage at which the ATOP is being completed;

3. Frame the interview:

Use a simple calendar to clarify what you mean by the last four weeks and as a prompt to help the client think back across this period. Week 4=past 7 days (usually); Week 3=7days before that….

4. Enter client responses:

- **Nil drug/alcohol use** – enter "00" in the total box
- **Timeline** – invite the client to recall the number of days in each of the past four weeks on which they did something
- **Quantities** - The average amount used on a typical using day during the past four weeks
  Agree unit of measure with your client.
- **Yes and No** – a simple tick for yes or no
- **Rating Scale** – a 0-10 scale where "0" is poor and "10" is good. Together with the client, **CIRCLE** a number.
- **Refused/can't recall** – write "NA" (short for Not Answered) next to the total box, tick box or rating scale.

5. Section 1 notes:

Question a: Use the Alcohol NHMRC Standard Drinks Chart to calculate standard drinks.

Question f: Examples of Other opioids include oxycodone, MS contin, Codeine, Street Methadone, Street Buprenorphine. Not included: Methadone and buprenorphine prescribed for the treatment of opioid dependence.

Question k: Injecting equipment includes needle, syringe, water, spoon, or filter.

6. Section 2 notes:

- Refer to manual for definitions of homelessness and risk of eviction.
- Before asking Items (f) to (h) remind the client about confidentiality issues (see box)

7. Business Rules

WHEN

Start of Service Episode

All clients complete an ATOP at the start of a new service unless the client has completed one in the past 28 days and you have accessed a copy of that ATOP.

Progress Review

Usually every 3 months, but see manual for details.

Discharge

OPT and **Counselling** clients should complete a discharge ATOP within two weeks either side of the planned discharge date.

REFERRAL when referring a client, for an additional service episode as part of the current treatment plan or to another service provider as part of discharge planning, send a copy of the most recent ATOP with the referral.

CONSENT it is good practice to share information with the other service providers during the care plan review. It is important that information is shared according to local protocols and that client is informed of this practice. Client consent to share information is not required if all service providers involved are working in the same Local Health District.

CONFIDENTIALITY

- The ATOP is treated in the same way as any other information held on your health record - it is protected by law from unauthorised access or use - any person who has access to this information is bound by a duty of confidentiality.
- The courts may subpoena health records and Community Services may request information in child at risk investigations.
- Where data is to be use used to evaluate how well the service is providing treatment, the information pulled from the database will be presented in a format in which individual clients can't be identified.

Section 2: Items (f) to (h)

- I'd like to remind you that the answers you provide to these questions are held on your health record and that courts may subpoena health records and Community Services may request information at child at risk investigations.
- However, I am not asking for any details - just general information about whether you did certain things. Please just answer "yes" or "no".

9 ATOP (v4 Feb 2013)

Surname: _____ Given Names: _____ MRN: _____

Date of Birth: ____/____/____ Sex: _____ ATOP DATE: ____/____/____

Treatment Stage ☐ Start of service episode ☐ Progress review ☐ Discharge ☐ Post Discharge

Affix patient Label Here

Section 1: Substance use

Record number of days used in each of the past four weeks	Typical qty on day used	Units	Week 4 (most recent)	Week 3	Week 2	Week 1	TOTAL
a Alcohol		Std drinks	0-7	0-7	0-7	0-7	0-28
b Cannabis			0-7	0-7	0-7	0-7	0-28
c Amphetamine type substances (eg. ice, MDMA etc.)			0-7	0-7	0-7	0-7	0-28
d Benzodiazepines (prescribed & illicit)			0-7	0-7	0-7	0-7	0-28
e Heroin			0-7	0-7	0-7	0-7	0-28
f Other opioids (not prescribed methadone/buprenorphine)			0-7	0-7	0-7	0-7	0-28
g Cocaine			0-7	0-7	0-7	0-7	0-28
h (i)Other substance			0-7	0-7	0-7	0-7	0-28
(ii)Other substance			0-7	0-7	0-7	0-7	0-28
i Daily tobacco use?					Yes ↕	No ↕	

Record number of days client injected drugs past four weeks (if no, enter zero and go to section 2)	Week 4 (most recent)	Week 3	Week 2	Week 1	TOTAL
j Injected	0-7	0-7	0-7	0-7	0-28
k Inject with equipment used by someone else?			Yes ↕	No ↕	

Section 2: Health and Wellbeing

Record days worked and at college, school or vocational training for the past four weeks	Week 4	Week 3	Week 2	Week 1	TOTAL
a Days paid work (incl. all paid work; not voluntary work)	0-7	0-7	0-7	0-7	0-28
b Days at school, tertiary education, vocational training	0-7	0-7	0-7	0-7	0-28

Record the following items for the past four weeks

c Have you been homeless?		Yes ↕ No ↕
d Have you been at risk of eviction?		Yes ↕ No ↕
e Have you, at any time in the past four weeks, been a primary caregiver for or living with any child/children	(i) under 5yo?	Yes ↕ No ↕
	(ii) 5-15yo?	Yes ↕ No ↕
f Have you been arrested?		Yes ↕ No ↕
g Have you been violent (incl. domestic violence) towards someone?		Yes ↕ No ↕
h Has anyone been violent (incl. domestic violence) towards you?		Yes ↕ No ↕

i Client's rating of **psychological health status** (anxiety, depression and problem emotions and feelings)

Poor 0 1 2 3 4 5 6 7 8 9 10 Good

j Client's rating of **physical health status** (extent of physical symptoms and bothered by illness)

Poor 0 1 2 3 4 5 6 7 8 9 10 Good

k Client's rating of **overall quality of life** (e.g. able to enjoy life, gets on well with family and partner, satisfied with living conditions)

Poor 0 1 2 3 4 5 6 7 8 9 10 Good

10 Appendix

Prevention and management of opioid overdose [29]

Deaths from opiate overdose are preventable. You can avoid overdose by knowing what puts you at risk, knowing the warning signs of overdose, and knowing what to do in an emergency. This information will also help you save another person's life if they overdose when you are with them.

Knowing what puts you at risk of an overdose

1. Using opiates when you are unsure of your tolerance

Your tolerance to opiates will drop quickly after a detox, or any break in using; if you use again when your tolerance is lower, your risk of overdose is much higher.

If you do start using opiates again after a break, don't inject with your tolerance down – you will get a big enough hit from smoking opiates.

You need to know that if you are on naltrexone and then you stop taking it and start using heroin (or other opiates) again, your risk of overdosing is very high.

2. Injecting opiates

You are at a much higher risk of overdose if you inject heroin rather than smoke it. If you do inject, you increase the risks of overdosing if you inject by yourself.

Injecting again if you have had a dirty or missed hit is risky. It takes time for drugs to be absorbed into the bloodstream. If you inject again, you increase the risks of overdose.

3. Taking more than one drug at a time

Using more than one downer-type of drug is extremely dangerous; never mix drugs like heroin, valium, temazepam and alcohol. The more downers and alcohol in someone's system, the smaller the amount of opiate needed to overdose.

Speed and cocaine can temporarily mask the sedative effects of opiates and other downer-type drugs. The speed and cocaine will wear off more quickly than the opiate and, if you injected more opiate than you thought, you could overdose.

Know the signs

People overdosing may:

- have pale skin, blue lips, blue fingernails;
- not wake up (or not react to loud noises);
- make gurgling, snoring or choking sounds;
- have shallow or disrupted breathing;
- have a slow or very faint pulse.

[29] Based on material developed by Drug and Alcohol Services South Australia

10 Prevention and management of opioid overdose (continued)

There can be a long delay between having a hit and the first signs of overdose – sometimes these may be hours later.

If a person cannot be easily woken, they may have overdosed. Nothing you do will bring them round. Call an ambulance, dial 000.

What to do if someone has an overdose

Don't panic.

1. Lie the person on the floor.
2. Put them in the Recovery Position (on their side with one arm bent and head back).
3. Call an ambulance, dial 000.
4. Do not leave them alone unless you go to get help yourself – if you have to leave them, make sure they cannot roll over onto their back.
5. When the ambulance arrives, if you can, tell them what they have taken. This could save their life.

There are lots of videos on You Tube showing how to put a person into the Recovery Position. Look and learn before you need to do it.

Calling an ambulance

If a person has overdosed, you must dial 000 for an ambulance immediately.

The quicker the ambulance arrives, the more likely you are to save the person's life.

When you dial 000 you don't have to mention a drug overdose. Just say you have found someone who has collapsed or is unconscious and they need an ambulance.

Ambulance services do not automatically call the police to an overdose so don't think twice before calling 000. The police believe that saving lives takes priority over any police enquiry. The police will only attend an overdose if the ambulance officers are in danger or fear violence.

Do not threaten ambulance officers.

Lock up any dogs.

If it is night, turn on outside lights or a car's hazard lights. If possible have someone outside to meet the ambulance.

11 Appendix

Further reading and resources

State and Territory Government Services

New South Wales

- Alcohol and Drug Information Service
  02 9361 8000 Metro; 1800 422 599 Rural
- Methadone Advice and Conciliation Service (MACS)
  1800 642 428 (9:30am-5pm Monday to Friday)
- Authorisation of prescribing and dispensing
  NSW: Pharmaceutical Services Branch, NSW Health
  Phone (02) 9859 5165, E-mail pharmserv@doh.health.nsw.gov.au
  Web: http://www0.health.nsw.gov.au/csqg/ps/index.asp

Victoria

- Directline
  1800 888 236 Metro; 1800 858 584 Rural
- Drugs & Poisons Controls in Victoria
  including links to Victorian policy on maintenance pharmacotherapy for opioid dependence and training programs for prescribers and dispensers
  http://www.health.vic.gov.au/dpcs/pharm.htm
  For health practitioners: 1300 364 545
- Drug and Alcohol Clinical Advisory Service
  1800 812 804; http://www.dacas.org.au/

Queensland

- Alcohol and Drug Information Service
  07 3236 2414 Brisbane; 1800 177 833 Statewide
- Drugs of Dependence Unit
  (07) 3328 9890; http://www.health.qld.gov.au/atod/ddu.asp

Western Australia

- Alcohol and Drug Information Service
  08 9442 5000 Metro; 1800 198 024 Rural
- Parent Drug Information Service
  08 9442 5050 Metropolitan; 1800 653 203 Rural
- Clinical Advisory Service
  08 9442 5042 Metro; 1800 688 847 Rural
- Drug and Alcohol Office
  http://www.dao.health.wa.gov.au/

11 Further reading and resources

South Australia

- Alcohol and Drug Information Service
  08 8363 8618 Metro; 1300 131 340 Statewide
- Information on prescribing drugs of dependence
  http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+topics/medicines+and+drugs/prescribing+medicines+regulations+and+requirements/prescribing+drugs+of+dependence
- Drugs of Dependence Unit
  1300 652 584; email drugsofdependenceunit@health.sa.gov.au
- Drug and Alcohol Services South Australia
  www.dassa.sa.gov.au
  Note: Website is in the process of being migrated to:
  www.sahealth.sa.gov.au
  Clinical Advisory Service (08) 8363 8633

Tasmania

- Alcohol and Drug Information Service
  03 6233 6722 Metro; 1800 811 994 Statewide
- Department of Health and Human Services, Pharmaceutical Branch
  Licence Application Forms (03) 6233 2064;
  http://www.dhhs.tas.gov.au/psbtas/licence_application_forms

Northern Territory

- Alcohol and Drug Information Service
  08 8922 8399 Darwin;
  08 8951 7580 Alice Springs;
  1800 131 350 Statewide

Australian Capital Territory

- Alcohol and Drug Information Service
  02 6207 9977
- Authorisation of prescribing and dispensing
  http://health.act.gov.au/health-services/population-health/health-protection-service/pharmaceutical-services/controlled-medicines
  Phone (02) 6205 0998

Commonwealth Government Services and Agencies

- Medicare Benefits Schedule
  www.mbsonline.gov.au
- Therapeutic Goods Administration
  Adverse effects of drugs: www.tga.gov.au/daen
  Product and consumer information: www.ebs.tga.gov.au
  Drugs in pregnancy: www.tga.gov.au/ and search for medicines in pregnancy database
  Drugs and overseas travel: http://www.tga.gov/au/consumers/travellers-leaving.htm

11 Further reading and resources

Commonwealth Government Services and Agencies (continued)

- AustRoads (Fitness to drive)
  www.austroads.com.au
- Australian National Council on Drugs
  Principal advisory body to government on drug policy; website includes links to a number of publications and reports: http://www.ancd.org.au/
- National Drug Strategy
  Cooperative venture between the Commonwealth and State/Territory governments as well as the non-government sector. A wide range of publications can be accessed through the website:
  http://www.nationaldrugstrategy.gov.au/

National Services

- Family Drug Support – Telephone support to families in crisis due to drug and alcohol issues. Staffed by volunteers who have first hand experience of drug dependent family members.
  1800 368 186 or www.fds.org.au
- Beyond Blue
  1300 22 4636 or www.beyondblue.org.au
- CounsellingOnline
  1800 888 236 or www.counsellingonline.org.au
- DrugInfo
  1300 85 85 84 or www.druginfo.adf.org.au
- Kids Help Line
  1800 551 800 or www.kidshelp.com.au
- Family Drug Helpline
  9am-9pm, Monday to Friday
  1300 660 068 or www.familydrughelp.org.au
- Lifeline
  131 114 or www.lifeline.org.au
- Narcotics Anonymous
  1300 652 820 or www.na.org.au
- Quitline
  8am-8pm Monday to Friday
  13 18 48 or www.quitnow.gov.au
- SMART Recovery Australia
  02 9373 5100 or www.smartrecoveryaustralia.com.au

11 Further reading and resources

National Organisations

- The Alcohol and other Drugs Council of Australia (ADCA) is the non-government national peak body representing the interests of the alcohol and other drugs sector. Useful resources on their website include a page of links to help lines and other services in States and Territories, as well as national services.
  See http://www.adca.org.au/help-lines-services
- Australasian Society for HIV Medicine (ASHM)
  A peak organisation of health professionals in Australia and New Zealand who work in HIV, viral hepatitis and sexually transmissible infections.
  www.ashm.org.au
- Australasian Professional Society on Alcohol and Other Drugs (APSAD)
  The leading multidisciplinary organisation for professionals involved in the alcohol and other drug field in the Asia-Pacific region. APSAD publishes the journal Drug and Alcohol Review and holds an annual conference
  www.apsad.org.au

Useful documents and websites

- National Medicines Policy and Quality Use of Medicines

Australia's National Medicines Policy is a cooperative endeavour to bring about better health outcomes for all Australians, focusing especially on people's access to, and wise use of, medicines. The term "medicine" includes prescription and non-prescription medicines, including complementary healthcare products. The Policy has four central objectives: timely access to the medicines that Australians need, at a cost individuals and the community can afford; medicines meeting appropriate standards of quality, safety and efficacy; quality use of medicines; and maintaining a responsible and viable medicines industry. For more information go to http://www.health.gov.au/internet/main/publishing.nsf/Content/nmp-objectives-policy.htm

Quality Use of Medicines (QUM) is one of the central objectives of Australia's National Medicines Policy.

QUM means selecting management options wisely; choosing suitable medicines if a medicine is considered necessary; and using medicines safely and effectively.

The definition of QUM applies equally to decisions about medicine use by individuals and decisions that affect the health of the population.

The term 'medicine' includes prescription, non-prescription and complementary medicines. For more information go to
http://www.health.gov.au/internet/main/publishing.nsf/Content/nmp-quality.htm

Database of interactions between methadone, buprenorphine and other drugs
www.opioiddruginteractions.com

Information on drugs known to prolong QTc interval
www.qt.com

11 Further reading and resources

Useful documents and websites (continued)

National clinical guidelines on the management of drug use in pregnancy
http://www0.health.nsw.gov.au/pubs/2006/ncg_druguse.html

RACGP guidelines on management of pain
www.racgp.org.au/your-practice/guidelines/silverbook/common-clinical-conditions/pain-management/#1

The Cochrane Library
Full text of Cochrane reviews can be accessed free from any computer in Australia from www.thecochranelibrary.com

International availability of opioid substitution treatment
http://www.indro-online.de/travel.htm

National Treatment Agency, UK (now part of Public Health England)
For links to publications, go to http://www.nta.nhs.uk/publications.aspx

Index

Index

Index