

**OPERATIONAL  
GUIDELINES FOR THE  
MANAGEMENT OF  
OPIOID DEPENDENCE  
IN THE SOUTH-EAST ASIA REGION**



Operational  
guidelines for the  
management of  
opioid dependence  
in the South-East Asia Region



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## Preface

The South-East Asia Region is home to nearly 3.4–5.6 million injecting drug users, a large proportion of whom resort to unsafe injecting practices such as sharing of needles and syringes. These practices and related risk behaviours have led to a rapid and large-scale transmission of HIV and hepatitis C among this population. The prevalence of HIV among injecting drug users in some countries of the Region exceeds 30% and that of hepatitis C virus ranges between 50% and 95%.

In order to prevent new infections, countries need to urgently expand the implementation of evidence-based drug treatment interventions and make full use of all therapeutic options for managing drug dependence and reducing harms from unsafe injecting. Opioid substitution therapy (OST) is the most useful and cost-effective intervention for managing opioid dependence and reducing the harms associated with it.

OST is now available in India, Thailand, Indonesia, the Maldives and Nepal, and will soon be introduced in Bangladesh. While these services still have very low coverage, the increasing acceptance of OST by Member States has highlighted the need for standardized and operational guidance to health staff in order to be able to deliver quality OST.

These guidelines are based on the World Health Organization's *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence* (Geneva, 2008); *Guidelines on methadone in Myanmar for prescribers and dispensers* (Department of Health, Ministry of Health, Union of Myanmar and WHO, 2004); and *Regional guidelines for drug detoxification in closed settings* (Manila, World Health Organization Regional Office for the Western Pacific, 2008) unless otherwise referenced.

The purpose of these guidelines is to assist physicians and drug treatment professionals to establish and deliver evidence-based, good quality, effective OST services in South-East Asia. These are intended to be operational guidelines rather than a detailed discussion of the literature.

## Acronyms and abbreviations

3TC	lamuvidine
ABC	abacavir
AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
ATS	amphetamine-type stimulants
ATV	atazanavir
ATT	antituberculosis treatment
AUDIT	Alcohol Use Disorders Identification Test
AZT	zidovudine
CBT	cognitive-behavioural therapy
CNS	central nervous system
CPR	cardiopulmonary resuscitation
d4T	stavudine
ddI	didonasine
DOT	directly observed treatment
EC	enteric coated
EFV	efavirenz
FTC	emtricitabine
HIV	human immunodeficiency virus
IDU	injecting drug user
IM	intramuscular
IV	intravenous
LPV	lopinavir
MMT	methadone maintenance therapy
NAS	neonatal abstinence syndrome
NASS	neonatal abstinence syndrome score
NGO	nongovernmental organization
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NVP	nevirapine
OST	opioid substitution therapy
PI	protease inhibitor
RTV/r	ritonavir
SC	subcutaneous
SQV	saquinavir
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNGASS	United Nations General Assembly Special Session
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization

## Glossary

<b>Abstinence</b>	Refraining from drug use whether as a matter of principle or for other reasons
<b>Addiction</b>	<i>See</i> “dependence”. The term “addiction” was more commonly used in the past and has to large extent been replaced by “dependence” as it is considered stigmatizing. It refers to repeated and compulsive use of a psychoactive substance or substances despite knowledge of the negative consequences.
<b>Agonist</b>	A drug that binds to and activates a particular type of receptor. It produces effects similar to those of a substance/drug.
<b>Analgesic</b>	A substance that reduces pain and may or may not have psychoactive properties
<b>Antagonist</b>	A drug that blocks a particular type of receptor in the brain, preventing it from being activated. Pharmacologically, an antagonist interacts with a receptor to inhibit the action of agents (agonists) that produce specific physiological or behavioural effects mediated by that receptor. For example, naltrexone is an opioid antagonist, meaning it blocks and prevents activation of the opioid receptors.
<b>Brief intervention</b>	A treatment strategy in which structured therapy of short duration (typically 5–30 minutes) is offered with the aim of assisting an individual to cease or reduce the use of a psychoactive substance or (less commonly) to deal with other life issues
<b>Buprenorphine</b>	A partial opioid agonist used for the treatment of opioid dependence. <i>See also</i> Appendix B.
<b>Cirrhosis</b>	A severe liver condition characterized by destruction of liver cells and replacement with scar tissue. Liver function is markedly reduced.

Closed settings	Refers to any institution or centre where people are detained and not able to leave. Examples of closed settings include compulsory drug treatment centres and prisons.
Dependence	A syndrome characterized by compulsive use of a substance despite knowledge of the negative consequences of such use. <i>See also</i> “addiction”, and Section 6.3.2 (p. 19)
Detoxification	The process by which an individual is withdrawn from the effects of a psychoactive substance. Detoxification may or may not involve the administration of medication.
Drug half-life	The time the body takes to remove 50% of an administered medication
Dual diagnosis	A general term referring to co-morbidity or the co-occurrence in the same individual of a psychoactive substance use disorder and another psychiatric disorder
Human immunodeficiency virus (HIV)	The virus that causes AIDS. HIV is transmitted through blood, semen, vaginal fluid and breast milk. There are treatments available to prevent HIV from progressing to AIDS, but as yet there is no cure or vaccine.
Maintenance treatment	Long-term provision of medication with the same or similar action as the patient’s drug of dependence. The goal is to reduce illicit drug use and the harms occurring from it.
Methadone	A synthetic opioid drug used in maintenance therapy for those dependent on opioids. It has a long half-life, and can be given orally once daily with supervision. <i>See also</i> Appendix B.

Motivational interviewing	A style of interviewing that aims to increase a patient's motivation to change his or her behaviour
Naltrexone	An opioid antagonist used to prevent relapse in drug-dependent individuals. <i>See also</i> Appendix B.
Neuroadaptation	The neuronal changes within the brain associated with both tolerance and the appearance of a withdrawal syndrome
Neurotransmitter	A chemical released in the brain that blocks or activates brain receptors
Opiate	One of a group of naturally occurring alkaloids derived from the opium poppy ( <i>Papaver somniferum</i> ), which activates opiate receptors in the brain and has the ability to induce analgesia, euphoria and, in higher doses, stupor, coma and respiratory depression. The term opiate includes heroin and morphine and excludes synthetic opioids.
Opioid	The generic term applied to alkaloids from the opium poppy ( <i>Papaver somniferum</i> ), their synthetic analogues, and compounds synthesized in the body, which interact with the same specific receptors in the brain, have the capacity to relieve pain, and produce a sense of well-being (euphoria). The opium alkaloids and their synthetic analogues also cause stupor, coma and respiratory depression in high doses. Examples include codeine, methadone, buprenorphine and (dextro)propoxyphene.
Peer educator or peer facilitator	Peer education typically involves using the members of a given group to effect change among other members of the same group such as modifying their knowledge, attitudes, beliefs or behaviours. A peer educator helps group members define their

concerns and seek solutions through the mutual sharing of information and experiences. A peer educator not only tells the peers about a desired risk reduction practice but also models it.

**Pharmacotherapy**

The use of pharmacologically active medication to treat a condition. In the case of opioid dependence it refers to opioid substitution therapy, which is also known as opioid pharmacotherapy.

**Polysubstance use**

The concomitant use of multiple psychoactive substances. Also called multiple substance (or drug) use

**Problematic substance use**

The use of psychoactive substances resulting in negative consequences for the individual

**Psychoactive substance**

A substance that, when ingested/inhaled/injected, affects mental processes, e.g. cognition or affect

**Relapse**

A return to drug use by a formerly dependent person after a period of abstinence, often accompanied by reinstatement of dependence symptoms. Some distinguish between relapse and lapse (“slip”), with the latter denoting an isolated occasion of drug use. Relapse is very common and most drug users relapse several times before they achieve long-term abstinence.

**Route of administration**

The way in which a substance is introduced into the body, such as by oral ingestion; intravenous (IV), subcutaneous, or intramuscular (IM) injection; inhalation; smoking

**Substitution**

Substitution means replacing the harmful opioid of dependence, commonly heroin or buprenorphine in the South-East Asia Region, with a less harmful opioid.

Therapeutic community	An approach to drug treatment in which individuals with psychoactive substance use disorders live in a structured environment in order to achieve rehabilitation. Such communities often operate under strict rules and are frequently geographically isolated. As well as attending therapeutic activities, patients take responsibility for the general running of the community.
Throughcare	The continued provision of care to a detainee from a closed setting after the detainee enters the community
Tolerance	A decrease in response to a drug dose that occurs with continued use. Increasing doses of drugs are required to achieve the effects originally produced by lower doses.
Withdrawal	A group of symptoms of variable clustering and degree of severity which occurs on cessation or reduction of use of a psychoactive substance that has been taken repeatedly, usually for a prolonged period and/or in high doses. The syndrome may be accompanied by signs of physiological disturbance. A withdrawal syndrome is one of the indicators of a dependence syndrome.



# INTRODUCTION

The purpose of these guidelines is to provide a framework for evidence-based clinical practice to prescribers and other health professionals involved in the management of opioid dependence in South-East Asia. These guidelines have been developed in accordance with the World Health Organization's (WHO) *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*, mindful of the context of opioid dependence and its treatment in the Region.<sup>1</sup>

## 1.1

### The context of opioid dependence in South and South-East Asia

The South and South-East Asia Region is home to nearly 3.4–5.6 million injecting drug users.<sup>2</sup> The Region saw a transition in the 1990s from non-injecting use of mostly opium to heroin and other pharmaceutical drugs including buprenorphine, (dextro)propoxyphene, benzodiazepines and, in some cases, antihistamines. Polysubstance use as well as “cocktailing” of drugs (usually a mixture of buprenorphine, benzodiazepines and antihistamines) is widespread in the Region. The use of amphetamine-type stimulants (ATS) is also a key concern in many countries of South-East Asia, although the prevalence of ATS injecting remains relatively low at the moment.

Related to the diffusion of injecting drug use is the rapid and large-scale transmission of HIV and hepatitis C among those using unsterile injection practices. Prevalence of HIV in this population in Indonesia, Thailand, Myanmar, large parts of India and Nepal exceeds 30%, while in Bangladesh prevalence is approaching 10%. Injecting drug use and related risk behaviours and harms are also an emerging concern in the Maldives and Bhutan.

The prevalence of unsafe injecting remains high despite the increase in availability of needle/syringe programmes, and there is an urgent need for countries to expand the implementation of evidence-based drug treatment interventions and make full use of all therapeutic options for managing drug dependence and reducing harms from injecting. The most useful and cost-effective intervention for managing opioid dependence and reducing the harms associated with it remains opioid substitution therapy (OST). Rigorous scientific studies have confirmed that OST reduces both unsafe injecting and sexual practices, and has many additional benefits such as reducing involvement in crime and improving social functioning.

At present, OST is available in India, Indonesia (including in some prisons), Thailand and Nepal, but its coverage is very limited. Implementation of OST is also planned for the Maldives and Bangladesh in the very near future. Therefore, there is a need for regionally relevant guidelines which will assist in training and supporting physicians and drug treatment professionals in the delivery of good-quality, effective and scaled-up OST services.

## 1.2 Opioid dependence and harm reduction

The term harm reduction refers to policies, programmes and projects that aim to reduce the health, social and economic harms associated with the use of psychoactive substances. It is an evidence-based and cost-effective approach, bringing benefits to the individual, community and society.<sup>3,4</sup>

In the context of dependent or harmful opioid use, harm reduction means preventing the transmission of HIV and hepatitis B and C through sterile injection practices, reducing injection-related injuries through safe injection techniques, and reducing engagement in illegal activities through the use of methadone and buprenorphine.<sup>5</sup> As OST has demonstrated effectiveness in reducing unsafe injecting and sexual risk behaviour, it is a key component of any harm reduction intervention.

The policy of harm reduction is endorsed by the United Nations, the United Nations General Assembly Special Session (UNGASS) 2006,<sup>6</sup> the G8,<sup>7</sup> and WHO, Joint United Nations Programme on HIV/AIDS (UNAIDS) and United

Nations Office on Drugs and Crime (UNODC).<sup>8</sup> Further information about effective harm reduction policies can be found elsewhere.<sup>8–12</sup>

## 1.3 Opioid dependence and its treatment

Opioids remain the most commonly injected psychoactive substance across Asia, despite the rise in amphetamine use in recent years. All opioids are associated with dependence. Common opioids of dependence in the Region are heroin, buprenorphine, (dextro)propoxyphene, opium and morphine. The route of administration is not relevant to the diagnosis of dependence, though more harm is associated with injecting than smoking or ingestion. The use of opioids as a component of polysubstance use is also becoming more common.

Opioids create the potential for dependence due to the acute euphoria, sedation and analgesia they induce, as well as the marked withdrawal syndrome that develops after the effect of the compound has ceased. Adaptations following chronic opioid use occur within the brain which compensates for these effects – called neuroadaptation. As a result, an individual may need to continue to use in order to feel “normal”. Long-term opioid use affects the brain’s reward system, a collection of brain structures that attempt to regulate and control behaviour by inducing pleasurable effects in such a way that individuals are unable to modify their drug use even in the face of significant adversity. These substantial personal difficulties include poor health, acquiring HIV and hepatitis C and B, breakdown of relationships, and other social and occupational consequences. Problematic opioid use and the development of dependence are thus medical conditions characterized by a series of symptoms and a predictable natural history for which treatment options now exist.

Opioid dependence is characterized by a strong desire or compulsion to take opioids, tolerance for the effects of opioids, the presence of a withdrawal state, neglect of other activities and continued use despite the knowledge and recognition of overtly harmful consequences. Opioid dependence develops over a period of time, usually weeks to months, and is associated with increasing frequency of use. The dependence syndrome is a well established entity in the medical literature. Further information is detailed in Section 6.3.2 (p. 19). In recent years, there has been an expansion of the treatment options for

opioid dependence. While agonist and partial agonist maintenance treatments (methadone and buprenorphine, respectively) are increasingly recognized to be the most effective management strategies, there are also increased options for opioid withdrawal and relapse prevention. The expanded range of treatment options provides greater choice for the treatment of opioid dependence and is likely to attract more patients as a result. In practice, different approaches will suit different patients, and many patients will undergo several episodes of different forms of treatment to form their own conclusions on treatment effectiveness.

## 1.4 Opioid substitution therapy

Opioid substitution therapy is an effective, evidence-based intervention highly recommended by WHO and other United Nations agencies to prevent HIV transmission among drug injectors and to treat drug dependence.<sup>5,8</sup> It “involves the administration of a long-acting opioid drug to an opioid-dependent person, usually by a non-parenteral route of administration, for the therapeutic purposes of preventing or substantially reducing the injection of illicit opioids such as heroin. Its goal is to improve the health status and psychological and social well-being of the opiate-dependent person.”<sup>13</sup>

OST refers most commonly to methadone or buprenorphine and their various forms, although other medications such as heroin have been successfully used as replacement therapy for illicit opioid dependence. Substitution means replacing the harmful opioid of dependence, commonly heroin, with another opioid that causes less harm. The substitute opioid is normally taken in an oral form within a regulated environment under clinical supervision (as in directly observed treatment [DOT]) to prevent diversion or injecting and the need to use other opioid-based substances. OST is also known as opioid agonist therapy, agonist maintenance treatment, substitution maintenance therapy or opioid replacement therapy.

OST in the treatment of opioid dependence is effective in reducing illicit opioid use and injection frequency (hence transmission of HIV and hepatitis B and C). It also increases safe injection practices, reduces engagement in illegal activities, reduces the likelihood of incarceration and increases the likelihood

## Introduction

of employment.<sup>11</sup> All these factors together mean that OST stabilizes patients' lives, providing substantial benefits for patients, their families and the broader community.

OST is more effective than withdrawal or opioid antagonist treatment in reducing illicit opioid use and retaining patients in treatment. Methadone maintenance is the most effective treatment for opioid dependence, characteristically producing a greater reduction in illicit opioid use, and a longer retention in treatment than buprenorphine. Higher-dose methadone is more effective than lower-dose maintenance regimens. Methadone is generally substantially cheaper than buprenorphine.



## 2

# TREATMENT SERVICES AND SYSTEMS

Several different types of services and treatments have been developed for substance use disorders. These can be broadly categorized as follows:

- “Open access” services:
  - advice, education, information, early intervention programmes
  - needle/syringe exchange programmes (in some nations)
- “Structured” services:
  - prescribing interventions (inpatient and outpatient/community settings)
  - community-based psychosocial counselling and relapse prevention
  - residential rehabilitation programmes.

It is common for a treatment programme to contain several different therapeutic components linked together (e.g. methadone maintenance with cognitive–behavioural psychotherapy [CBT]).

An understanding of the epidemiology of injecting drug use locally and across regions, states or provinces is important to inform planning of any treatment system or service. This should include an understanding of the types of drugs used and the demographics of the affected population. There are a number of techniques described elsewhere which can be used together to build an understanding of drug use patterns.<sup>14</sup> A needs assessment should be carried out to estimate the current and/or future nature and prevalence of substance use disorders in a specific population. Concurrently, an evaluation of the available health systems infrastructure and resources for drug dependence treatment can be useful to identify gaps between current health services and the needs of the affected population.<sup>15,16</sup> In order to minimize this gap and develop adequate

and effective services, sustained advocacy with policy-makers and planners is crucial.

Effective management of opioid dependence in a public health context requires adequate health systems infrastructure with human and capital resources distributed to reflect the needs of the communities. In South and South-East Asia, there is great variation in health infrastructure and health system responses to effective management of opioid dependence vary considerably. Drug treatment services are also offered in a wide variety of contexts in the Region, including in government drug dependence treatment clinics, mental health institutions, by nongovernmental organizations (NGOs), and in prisons and involuntary camps. Despite this variation in settings, there are several components that are fundamental in any system and these are addressed in the following chapters.



## 3

# ACCESS TO SERVICES

An effective public health approach to opioid dependence should include OST which is affordable and convenient to access. Access includes the ability to be assessed and provided with a treatment plan, as well as to being able to obtain the medication itself. Where possible, OST services should be located centrally and in proximity to drug use “hot spots”. Special attention should also be paid to opening hours and other operational issues that have a direct impact on physical, economic and psychological access.

### 3.1 Arrangements for dispensing

Prescribers should attempt to develop strong professional relationships with those dispensing pharmacotherapy to their patients. Dispensers generally see patients more often than medical practitioners and can provide useful advice about patient progress.

Dispensing may occur within a drug treatment centre, at a hospital pharmacy or at a community dispensing site. Dispensing may also occur within a closed setting. The hours of availability should suit the needs of the patients. For example, opening early in the morning facilitates those who have employment commitments.

Health professionals dispensing pharmacotherapy should ideally be trained in the management of opioid dependence.

### 3.2 Arrangements to cover the prescriber’s absence

Absence should ideally be arranged in advance so another medical practitioner can maintain patients already on treatment. Adequate and legible medical notes

are crucial to reducing complications in this scenario. When another medical practitioner cannot cover absence, arrangements should be made with the dispenser and senior staff to continue patients on therapy, but with no changes to prescribing until the next appointment with the medical practitioner. Patients who develop complications while their medical practitioner is absent should be referred to a drug treatment centre or medical practitioner with experience in the treatment of substance dependence. In all cases, the dispenser and allied health staff involved in the care of patients should be contacted.

### 3.3 Cultural context

OST has been demonstrated as being effective independent of the cultural context. Despite this, the delivery of drug treatment services happens within a local sociocultural milieu and providers need to be cognisant of particular beliefs and practices specific to the local area in order to promote engagement and facilitate community acceptability. For example, dispensing hours of OST clinics may need to be changed during Ramadan, in order to facilitate continued therapy for those who are fasting.

### 3.4 Dosing fees

Many argue that opioid pharmacotherapy should be free to encourage uptake, while others argue that attaching a minimal fee to the medication can put greater value on the therapy. Whatever the case, the main determinant should be to maximize access to and retain the affected population in treatment.

If a dosing fee is charged, it should be kept to a minimum to allow equity of access and be consistent with the socioeconomic situation of patients. Dosing fees should always be flat so that economic incentives are not involved in clinical decision-making. For example, the cost to a patient of 20 mg methadone should be the same as 100 mg methadone.

### 3.5 Integrated service provision

An integrated approach to treatment means providing a patient-centred approach. For example, in areas where HIV is commonly acquired through

drug use, HIV and drug treatment services should be co-located. Co-location of these and other services such as DOTS for tuberculosis (TB), HIV testing and counselling, treatment for sexually transmitted infections (STIs) and drug user drop-in centres can facilitate management of co-morbid conditions and increase accessibility to these services.

## STAFFING

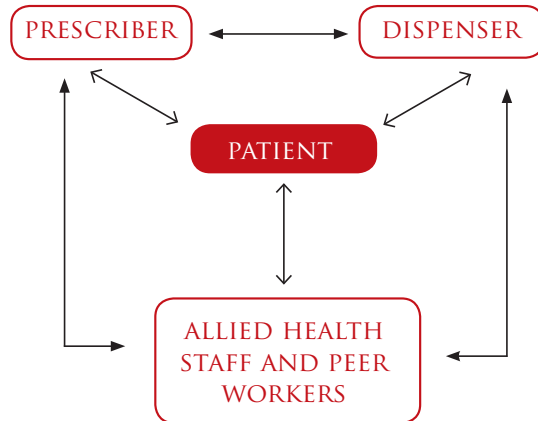
Human resources are often limited in drug treatment agencies, and ideal staffing profiles are seldom achieved. Efficient staffing profiles should reflect the diversity of the patient population and treatment setting, and make effective use of each member of the treatment team.

Every facility should have some trained physicians as they are required for prescription of pharmacotherapy. They should also play a leading role in the assessment and diagnosis of opioid dependence, and discussions around treatment matching, i.e. deciding on the type of treatment that would best suit an individual patient. In specialist clinics, medical staff should be supervised by a specialist in the treatment of substance dependence. In generalist settings, general practitioners or family medical practitioners and other medical staff should have a minimum level of training in the diagnosis and treatment of opioid dependence.

Trained nursing staff or doctor's assistants can attend to the screening of patients for injection-related injuries, bloodborne virus infections and STIs. They can also assist with substitution treatment dosing.

Social workers and other allied health staff are a very useful component of a treatment team and can provide counselling and other psychosocial interventions. In some settings, allied health staff may assist with finding temporary accommodation or employment for treatment seekers.

Depending on the treatment setting, a pharmacist may or may not be part of the team. In the case that methadone is being dispensed at the treatment site, pharmacist services are required. Dispensing pharmacists see patients almost every day and so develop strong relationships with patients. This allows patients' progress to be tracked on a daily basis.



**Figure 1.** Relationship of health providers to the patient

Peer educators and peer counsellors can provide an important bridge between health professionals and patients. Peers with leadership and counselling potential should be identified early and given the opportunity to train in a hands-on manner. Patients often listen to their peers more than to clinicians and so health professionals need to also develop good relationships with peer workers. This promotes the transfer of accurate information and knowledge to the patients themselves. Peers often commence their association through volunteering or being a patient of the service. They can be a useful adjuvant to health professionals in resource-poor settings with limited budgets.

#### 4.1 Staff mix in resource-limited settings

There is substantial socioeconomic and infrastructure variation within and between countries in the Region. In resource-limited settings, ideal staff mixes may not be available and the clinical capacity of staff and services may also be limited. In these situations, a basic staff profile is necessary to ensure adequate care. This includes

1. A prescriber, usually a medical practitioner
2. A dispenser to ensure supervised dosing, usually a pharmacist or a nurse
3. An allied health staff as an initial point of contact and “go-between” for the clinical staff and the patient. This can be trained peer worker(s) or a social worker or psychologist.
4. Administration staff as necessary.

This initial structure is adequate to ensure basic care. The addition of funding to this mix should be geared towards employing further allied health staff or peer workers followed by nurses, followed, if necessary, by further medical support. Medical practitioners are often employed on a part-time basis, while allied health staff, peer workers and a pharmacist or nurse are usually full time. When recruiting staff, special attention must be given to gender issues as women injecting drug users (IDUs) are often stigmatized more than men. Women may be reluctant to access facilities that do not employ female staff. Services should be aware that the gender balance of their staff should, where possible, reflect the gender profile of their clients. Some services may wish to explore female-specific service provision to encourage access by female patients.

#### 4.1.1

##### Consultation mechanisms for difficult clinical problems

In addition to an appropriate staff mix, services should ensure that mechanisms are available in the case of consultation for difficult clinical scenarios. This includes senior medical, nursing and allied health colleagues. Colleagues appropriate for consulting may be located at larger organizations within the same town though in some cases consultation may be needed with colleagues in larger urban centres. It is important that local staff (of all disciplines) develop strong professional relationships with these senior staff over time and that senior staff who act as clinical consultants have an understanding of the local context they are providing advice within.

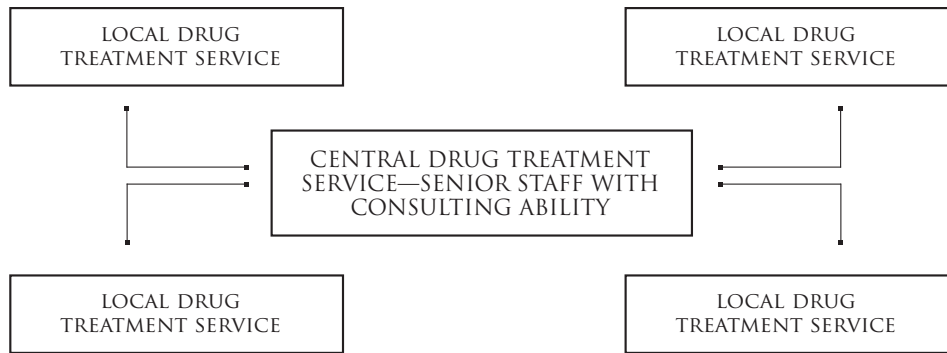
#### 4.2

##### Training and approval for prescribers

Training should consist of two phases

1. Initial training in the treatment of opioid dependence using pharmacotherapies
2. Ongoing professional development intermittently during the course of normal practice, which should include consulting more senior staff on complex problems among patients.

A national or provincial system of accreditation of medical practitioners in the treatment of opioid dependence using pharmacotherapy is recommended.



**Figure 2.** Relationship of local drug treatment services with senior centrally located consulting services

In some jurisdictions, medical practitioners are registered as being able to prescribe opioid pharmacotherapy. In many countries across the Region, this is not the case. Training and professional development systems should ensure that training is consistent and comprehensive, even if systems are not uniform across provinces and nationally.



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## PREVENTING ADVERSE EVENTS ON TREATMENT

# 5



Adverse events can and do occur on treatment. Many are preventable. Key steps to avoid adverse events on treatment are

- Patient education
- Training for staff
- Knowing drug interactions, particularly of methadone, benzodiazepines, and TB and HIV medications (*see* Appendix E)
- Taking special care in the case of
  - Liver disease or hepatitis
  - HIV – due to possible interactions between antiretroviral drugs (ARVs) and methadone/buprenorphine (*see* Appendix E)
  - Elderly patients
  - Polysubstance use (to prevent overdose)
- Regular patient review, which will be determined by patient progress. Poor progress should indicate more frequent review.



# 6

## ASSESSING SUITABILITY FOR TREATMENT

Assessing suitability for treatment should be carried out in a consistent manner from patient to patient to reduce error. Clinical protocols can enhance consistency. Although an assessment can be completed by any trained clinical staff, generally the diagnosis of opioid dependence should be made by the doctor (*see* Appendix A).

In practice, assessment of a new patient may take more than 45 minutes, while reviews can be substantially shorter. In order to ensure quality of services, medical practitioners may have to limit the number of patients they see in a day.

### 6.1 Confirm the identity

It is important to confirm that the patient is who they say they are. This is usually best done using a national identity card (such as a voter card, driving licence or ration card). However, in the Region, this is frequently not possible as many drug users are homeless and marginalized. Where an individual is not able to furnish proof of identity, the treatment centre should consider generating an identity card for the purposes of treatment. This has the added benefit of reducing harassment of patients by law-enforcement agencies.

### 6.2 Establish an effective therapeutic relationship

A strong therapeutic relationship with the patient is crucial to effective treatment. This is particularly important as many drug users are uncomfortable while giving a history of drug dependence. Successfully engaging patients can help them feel at ease and assist in gathering a complete history. Displaying empathy, sensitivity, regard and warmth towards the patient, and being aware

of the cultural context will help in building a rapport with the patient. Rapport should be based around respect, knowledge and the willingness to work through issues in a systematic fashion.

Clinical decision-making should, where possible, be an agreement between the patient and practitioner to maximize adherence to therapy. The extent to which this occurs may depend on the local context.

## 6.3 Assess suitability for treatment

Suitability for treatment of opioid dependence is determined by diagnosis and assessment. A diagnosis which leads to pharmacotherapy as treatment should be made by trained medical personnel.

### 6.3.1 Assessment

The following issues should be covered:

History	Key components
Current and past drug and alcohol use <ul style="list-style-type: none"> <li>• Opioids</li> <li>• Amphetamines</li> <li>• Benzodiazepines</li> <li>• Alcohol</li> <li>• Other drugs commonly used locally</li> </ul>	Type of drug Age at first use Age at daily use Current use amount/frequency Age at first injection Current and past treatment
Mental health including <ul style="list-style-type: none"> <li>• Depression</li> <li>• Anxiety</li> <li>• Mania</li> <li>• Psychosis</li> <li>• Self-harm</li> </ul>	Past episodes Current and past treatment
Co-morbid medical conditions	Viral hepatitis and chronic liver disease Injecting-related injury and disease HIV infection TB
Psychosocial issues	Living conditions Legal issues including history of incarceration Employment Educational status Family and relationship support Other cultural issues

Physical examination	Key components
Injection marks, inflammation, infection or vascular damage associated with injecting sites, evidence of TB, opportunistic infections or liver disease	Cellulitis and abscesses, thrombophlebitis, septicaemia, musculoskeletal infections, endovascular complications, viral hepatitis, respiratory tract infections

Mental state examination	Key components
May reveal depression, anxiety, hypomania or a psychotic illness. Depression and anxiety are the most common psychiatric co-morbidities	Psychiatric disorders, substance use-related disorders

Recommended investigations
STI screening HIV testing and counselling Screening for viral hepatitis Pregnancy test Urinary drug screen* if available

\* Urinary drug screens may benefit diagnosis by confirming the presence of opioids or other drugs. There is generally a cost and time delay associated with this type of drug screen.

The medical history is the most important component of the examination and is dependent on an open dialogue between the patient and prescriber.

### 6.3.1.1 Brief interventions during assessment

The aim of a brief intervention is to help the patient understand that their substance use is putting them at risk and encourage them to reduce or give up their substance use.<sup>17</sup> Brief interventions can be conducted on any relevant topic during initial patient assessment. Key areas for brief intervention are:

- Risk behaviour (sharing needles and syringes, unsafe sex)
- Polysubstance use (being aware of the interactions between different drugs)
- Overdose (reducing risk)

### 6.3.2

#### Diagnosing opioid dependence

WHO defines **opioid dependence** as a syndrome consisting of the following:<sup>18</sup>

1. A strong desire or compulsion to take opioids
2. Difficulties in controlling opioid-taking behaviour
3. The development of opioid withdrawal syndrome on ceasing use, which is relieved by intentionally reusing opioids
4. Tolerance to the effects of opioids
5. Neglecting other normal activities in preference for taking opioids
6. Persisting use despite knowledge of serious harmful consequences.

**Harmful opioid use** is defined as a pattern of use which is damaging to health for which the criteria for dependence may not be met. Adverse consequences may be physical, psychological or social. Patients engaging in harmful use can also be candidates for OST.

In general, patients with a diagnosis of opioid dependence are suitable for either substitution or withdrawal therapy using OST. Those early in their career of opioid dependence (e.g. first year or two) may initially benefit from non-opioid detoxification regimens in combination with counselling. Chronic, opioid-dependent patients (e.g. after several years of dependence) will almost certainly need long-term substitution therapy.

### 6.4

#### Provide the patient with information about treatment

A strong therapeutic relationship will strengthen information exchange. All members of the treatment team should contribute to educating the patient about opioid dependence, its treatment and other relevant issues.

Patient information should be provided in the following forms:

- Verbal discussions including answering the patient's questions
- Written information such as pamphlets (noting the level of patient literacy)
- Posters on the walls of the treatment centre so that patients can read while they wait

- Relevant video displays that provide health promotion messages
- Where appropriate, and if infrastructure is available, patients may be referred to websites.

The following topics should be covered:

- A explanation about the causes of opioid dependence
- For methadone
  - Peak effect 2–4 hours after administration
  - Interacts with other sedatives (alcohol, benzodiazepines), anti-TB medications (rifampicin) and some HIV medications (particularly nevirapine and efavirenz)
  - May take several weeks to achieve a comfortable dose
- For buprenorphine
  - Can only start upon ceasing other opioids for between 6 and 24 hours.
  - Must be administered under the tongue – patient should wait until all the drug has dissolved
  - Peak effect 2–4 hours after administration
  - Interacts with other sedatives (alcohol, benzodiazepines) and some ARVs (particularly atazanvir and ritonavir)
  - May take several days to achieve a comfortable dose
- An explanation of expected behaviour during the treatment programme
- The expected duration of treatment (may not be clear initially)
- The cost of treatment
- How to avoid overdose during treatment, including harm reduction
- Information about other relevant services and referral where necessary
- The process of resolution of complaints during treatment
- The expectations of treatment.

## 6.5

### Consider the options for treatment

A diagnosis should lead to the development of a treatment plan. Options for the management of harmful opioid use and opioid dependence are psychosocial interventions, non-opioid withdrawal therapy, opioid withdrawal or opioid maintenance pharmacotherapy. Preference should be given to OST in patients with opioid dependence.

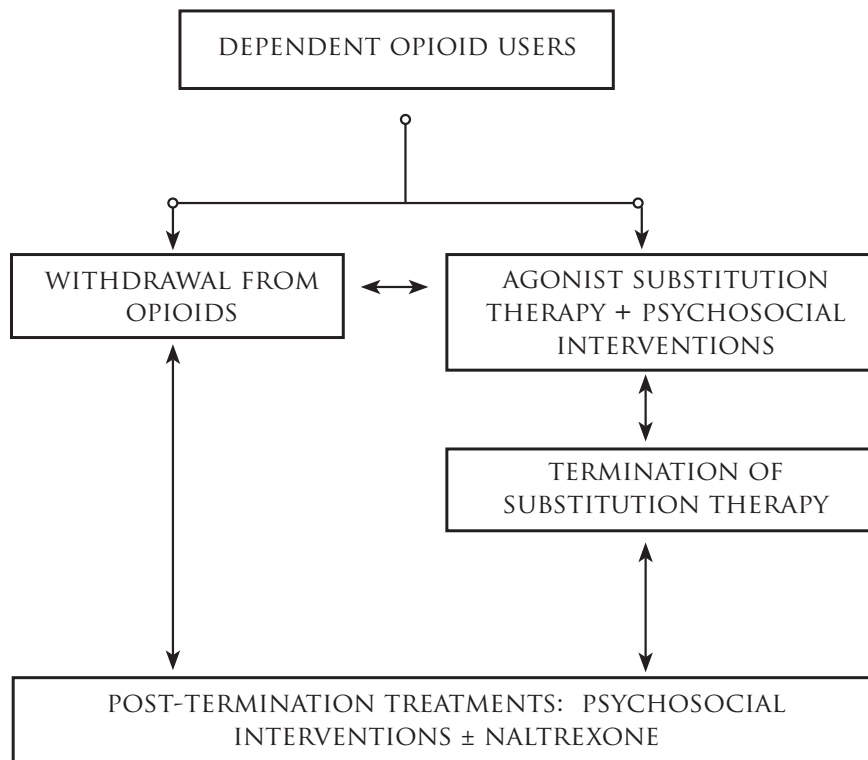


Figure 3. Treatment pathways for opioid dependence

There are several questions that should be answered prior to commencing treatment.

### 6.5.1 Does the patient need treatment?

A diagnosis of dependence or harmful substance use indicates that the patient is in need of treatment.

In the case that a person is engaging in non-problematic substance use such as occasional opium smoking in an elderly male in a rural area, a case might be made that treatment may not necessarily provide benefit. In such cases, it is important that patients are followed up to ensure that use does not become problematic or harmful.

## 6.5.2

### Psychosocial or pharmacological treatment (or both)

Psychosocial treatment is generally recommended as an adjuvant to all patients on pharmacotherapy. If a patient is to be given psychosocial treatment alone, it is important they have strong social support in place such as family or close friends. Given that many drug users are homeless and alienated from families and communities, this is frequently not easy to ensure.

Psychosocial intervention alone may be undertaken when the patient does not wish to commence on medication or where the harm resulting from the use of pharmacotherapy is greater than the resultant benefit. An example is a first episode of presentation to a drug treatment service by a young person with intermittent opioid use brought in by his family. Commencing this individual on methadone or buprenorphine may not necessarily benefit the person in this early phase.

## 6.5.3

### Substitution versus withdrawal

Most patients presenting for treatment of opioid dependence generally request withdrawal therapy in the false belief that when they have completed withdrawal they will be “drug-free” and able to get on with their lives. Families often reinforce this view. The rate of relapse following withdrawal from opioids is very high.

However, there are several reasons to provide a patient with withdrawal treatment:

1. It supports the patient in the decision to seek treatment.
2. It maintains engagement.
3. It reduces opioid use.
4. It allows the patient to remain abstinent.
5. It helps to stabilize people for commencement of ART or TB treatment and improves their health status.

Patients may unsuccessfully attempt withdrawal several times before embarking on substitution therapy.

OST is more successful than withdrawal at reducing illicit opioid use and retaining patients in treatment. Most patients with a history of opioid dependence benefit from substitution therapy to stabilize drug use and its consequences.

#### 6.5.4

#### Opioid pharmacotherapy versus non-opioid pharmacotherapy

Methadone and buprenorphine are the most common agents used for OST. Naltrexone, a medication that blocks the opioid receptors, has also been used to prevent relapse. Patients on naltrexone have a higher rate of relapse and are less likely to stay in treatment than those treated with methadone or buprenorphine. It is generally used successfully only in a small minority of patients who have employment, stable and supported social lives, and are highly motivated.

Withdrawal medication regimens can be opioid or non-opioid based. Buprenorphine is the preferred medication, though methadone can be used where buprenorphine is not available. Non-opioid regimens are less preferable to buprenorphine and more complicated, though they can be used where buprenorphine is not available.

#### 6.5.5

#### Methadone versus buprenorphine

This question is relevant only where both methadone and buprenorphine are available.

Patients may prefer one agent or the other. It is important to support patients in their decision unless there is a contraindication.

Methadone is cheaper and is preferable for OST, particularly in patients with co-morbid psychiatric issues, those who are less likely to adhere to therapy, those with co-morbid chronic pain or pharmaceutical opioid dependence (e.g. codeine or morphine) and where the sedative properties of methadone may be of benefit.

Buprenorphine may be preferable for higher-functioning individuals who need flexibility in dosing for employment purposes. Buprenorphine is less sedating than methadone. There is a view that buprenorphine is less desirable for those with a history of injecting buprenorphine. If an individual who is being prescribed buprenorphine continues to inject their prescribed dose, there is an argument that harm is not being reduced. In this case, it would be preferable to treat this patient with methadone or ensure strict supervision of buprenorphine administration. In these cases administration should, where possible, always be supervised and takeaway dosing discouraged except in extenuating circumstances.

## 6.6 Obtain consent for treatment

This may be done at any stage during the assessment process. Consent should be voluntary and include an explanation of the risks, benefits and expectations of treatment. Ideally, information should be provided in both verbal and written forms, mindful of the patient's literacy. Consent should be signed and dated by the patient.

Consent for minors or those under the age of 18 years should be given by a parent or guardian. If this is not possible, before commencing treatment the treatment team should seek appropriate information regarding significant adults or family members who have previously acted as guardian for the child.

## 6.7 Register the patient for OST

Each jurisdiction will have different methods of patient registration. Prescribers should be aware of local practices of patient registration. If there is no formal registration process, the drug treatment clinic should keep a database of patients registered with the organization, which should follow the general rules of privacy and confidentiality. This system should be readily accessible to the treatment team and contain:

- Name
- Date of birth
- Contact information

- Type and dose of initial pharmacotherapy
- Details of treating doctor and dispensing agency

In many settings where patients do not know their date of birth, have similar names and are homeless, a unique identifying code can be generated. This provides additional confidentiality for the patient and increases their confidence in seeking treatment (as many patients are in conflict with the law).

## 6.8 Consider precautions or contraindications

Methadone and buprenorphine are not suitable for people with decompensated liver disease (for example, cirrhosis with jaundice and ascites) as these drugs may precipitate hepatic encephalopathy and cause deterioration in the mental state. They may also worsen acute asthma and other causes of respiratory insufficiency.

Other **contraindications** listed by the manufacturers are: severe respiratory depression, acute alcoholism, head injury, raised intracranial pressure, ulcerative colitis, and biliary and renal colic.

**Precautions** for both include: high-risk polydrug use, mental illness, low levels of neuroadaptation to opioids (i.e. recent incarceration) and significant concomitant medical problems.

OST is preferred as best practice treatment in individuals with opioid dependence.

## 7.1 Methadone therapy

### 7.1.1 Careful induction and review during the first week

Patients should be counselled to not consume opioids or sedatives (including alcohol) for 24 hours prior to commencing methadone. The initial dose should be administered in the morning. The induction dose depends on:

- The severity of opioid dependence
- Use of other drugs such as sedatives

The maximum induction dose should be 30 mg. Patients should be reviewed 4 hours after the first dose for signs of withdrawal or intoxication in order to inform changes of dose in the first week of treatment. The maximum daily dose of methadone in the first week of treatment should be 40 mg. Doses should be increased every four days at a maximum, as methadone's long half-life means it takes five days for a change in dose to have its full effect.

**Table 1.** Recommended initial dose for methadone maintenance

Induction dose	Clinical condition
20 mg	Opioid dependence with polysubstance use or severe concomitant medical conditions
30 mg	Opioid dependence with minimal other drug use

Patients should be reviewed 3–4 days after the first dose. At this stage, it should be clear whether the initial dose needs to be increased. If the patient is experiencing withdrawal symptoms for most of the time, the dose can be

increased by a maximum of 10 mg. Withdrawal symptoms experienced only just before the next dose is taken to indicate that the dose may be increased by less.

### 7.1.2 Establish an effective substitution dose

Higher-dose methadone (more than 60 mg daily) is associated with better retention in treatment and greater suppression of illicit opioid use. Prescribers should aim to have most patients on 60–120 mg of methadone, guided by clinical assessment. This usually takes a few weeks.

The two most important aspects of clinical assessment in guiding dose changes are:

- The presence of withdrawal symptoms or signs of intoxication
- Illicit opioid use

The dose of methadone should be increased until the patient is not experiencing withdrawal symptoms but does not show signs of intoxication such as drowsiness or pinpoint pupils **and** illicit opioid use is generally less than weekly.

Doses should be increased by a maximum of 10 mg with at least four days separating each dose increase in order to reduce the risk of overdose. Evidence of intoxication should result in inquiries about other drug use (particularly alcohol or benzodiazepines) and, if necessary, a reduction in the methadone dose by 5–10 mg.

### 7.1.3 Review patient progress regularly

Patients should be reviewed regularly by all members of the treatment team. The team should discuss the patient's progress on at least two occasions in the first month of treatment and monthly thereafter.

Patients should be clinically reviewed on:

- Day 1, four hours after the first dose
- Day 3 or 4
- End of week 1

- At least weekly for the first month or until a stable dosage has been achieved
- At least every two weeks for the first three months of treatment
- At least monthly thereafter.

This schedule should be revised if a patient's condition deteriorates.

The purpose of review is to build a greater understanding of the patient's clinical and psychosocial issues, and develop a strong therapeutic relationship. Although length of treatment is usually an issue for patients, emphasis should be placed on clinical and psychosocial progress to determine the duration of treatment. Each review should also include the following:

<b>History</b>
Current methadone dose Current drug and alcohol use <ul style="list-style-type: none"> <li>• Opioids</li> <li>• Amphetamines</li> <li>• Benzodiazepines</li> <li>• Alcohol</li> <li>• Other drugs commonly used locally</li> </ul>
Co-morbid medical conditions <ul style="list-style-type: none"> <li>• Viral hepatitis and chronic liver disease</li> <li>• Injecting-related injury and disease</li> <li>• HIV infection</li> <li>• TB</li> </ul>
Important psychosocial issues
<b>Physical examination</b>
Signs of withdrawal or intoxication Signs of other medical conditions
<b>Mental state examination</b>
Screen for <ul style="list-style-type: none"> <li>• Depression</li> <li>• Anxiety</li> <li>• Mania</li> <li>• Psychosis</li> <li>• Self-harm</li> </ul>
<b>Management plan</b>
Modify management plan depending on review assessment

### 7.1.4

#### Side-effects of methadone

Side-effects are not uncommon on methadone. Patients should be educated about potential side-effects prior to commencing treatment and reminded about likely side-effects during treatment to allow early detection and management.

Key side-effects that should be discussed are:

- Sedation – particularly in combination with other sedatives
- Constipation – fluids and osmotic laxatives, e.g. lactulose, are the treatment of choice
- Sweating
- Nausea and possibly vomiting
- Reduction in libido
- Dry mouth.

### 7.2

#### Buprenorphine-based therapy

Buprenorphine-based therapies include buprenorphine alone or in combination with naloxone in a 4:1 ratio, both administered sublingually.

##### Precipitated withdrawal

Patients should be counselled to not consume opioids within six hours (or methadone within 24 hours) of the first dose of buprenorphine. Buprenorphine is a partial opioid agonist which binds tightly to the opiate receptor. It displaces other opioids from the receptor but only partially activates the receptor. The result is a precipitated relative withdrawal state. Although this precipitated withdrawal is not dangerous, it can be extremely uncomfortable and can result in the patient refusing treatment – the user returning to illicit opioids later that day to relieve the withdrawal symptoms.

### 7.2.1

#### Induction and review during the first week

The initial dose should be given in the morning after abstinence from short-acting opioids overnight and methadone for at least 24 hours. The patient should be reviewed 2–4 hours after the first dose for signs of withdrawal or intoxication. Buprenorphine dosing during initiation can be standardized as shown below.

Day	1	2	3	4
Dose (mg)	4	8	12	Variable

### 7.2.2

#### Establish an effective substitution dose

Achieving an optimal dose during buprenorphine substitution is simpler than with methadone. Doses can be increased by 2–4 mg daily until withdrawal symptoms and cravings have subsided. Patients are less likely to become intoxicated with buprenorphine as it only partially activates the opioid receptors. Most patients can be stabilized on 8–16 mg daily. The maximum daily dose during therapy is 32 mg.

In some countries of the Region, low-dose buprenorphine substitution is common practice (<4 mg daily). Indeed, recent buprenorphine guidelines for one country in South-East Asia recommend 4–8 mg as the optimal buprenorphine dose.<sup>19</sup> While substitution with low-dose buprenorphine is superior to no treatment, higher-dose buprenorphine has been found to be more effective than low-dose buprenorphine.<sup>1</sup>

Buprenorphine has a long half-life (37 hours), meaning that dosing can be less frequent than daily. Unlike methadone, it is a partial agonist so the effect of higher dosing reaches a ceiling after which higher doses result in a longer duration of action. The result is that after dose and clinical stabilization, patients can be dosed after two or three days.

**Table 2.** Buprenorphine dose equivalents in less-than-daily dosing

Dose frequency	Daily	every 2 days*	every 3 days*
Example dose with equivalent effect (mg)	8	16	24

\* Due to differences in metabolism, some individuals will need more than a triple dose to last 3 days. This is usually only an additional 2–6 mg. For example, an individual stabilized on 8 mg daily may need 30 mg to be comfortable for dosing every 3 days.

### 7.2.3

#### Review patient progress

Patients should be reviewed regularly by all members of the treatment team.

The team should discuss the patient's progress on at least two occasions in the first month of treatment and monthly thereafter.

Patients should be clinically reviewed on:

- Day 1, four hours after the first dose
- Day 3 – by this stage the likely stabilization dose should be reasonably clear
- End of week 1
- At least weekly for the first month or until a stable dosage has been achieved
- At least every two weeks for the first three months of treatment
- At least monthly thereafter.

This schedule should be revised if a patient's clinical condition deteriorates.

Each review should include the drug history, physical examination, mental state examination and the management plan modified accordingly (See section 7.1.3, p. 28).

### 7.2.4

#### Side-effects of buprenorphine

Buprenorphine has a better side-effect profile than methadone. Patients should be educated about potential side-effects prior to commencing treatment and reminded about likely side-effects during treatment to allow early detection and management.

Key side-effects that should be discussed are:

- Constipation – fluids and osmotic laxatives (e.g. lactulose) are the treatment of choice.

- Sedation – unlikely, but can happen particularly in combination with other sedatives such as benzodiazepines. A small minority of patients may find that buprenorphine acts as a stimulant, producing racing thoughts.
- Sweating
- Nausea
- Insomnia.

In addition, it is important for patients to be aware of the following two precautions regarding buprenorphine-based therapy:

- Other opioids are unlikely to work as effectively while a patient is taking buprenorphine. This is particularly important in the treatment of acute pain – consultation with a pain or substance-use treatment specialist is advised.
- Injection of the buprenorphine/naloxone preparation may result in a reduced effect from the buprenorphine or cause mild withdrawal symptoms.

The risk of overdose is lower for buprenorphine than methadone. Treatment of overdose, however, is more difficult as naloxone, an opioid antagonist which reverses opioid overdose, does not readily reverse the effects of buprenorphine. Overdose resulting in respiratory depression will need management in hospital using ventilation.

### 7.3 Writing prescriptions

Prescriptions should be written clearly and signed by the prescriber. The following information should be contained in the prescription:

- Name of the patient and another identifying piece of information such as the address or date of birth
- Type of treatment and dosage (some jurisdictions may require dosage to be written in numbers and words)
- Specific route of administration even though this is generally obvious
- Dates between which the prescription is valid
- All prescriptions should be written in milligrams (mg) to avoid confusion in dosing where methadone is mixed at variable concentrations.

An example of a prescription is given in Appendix C.

## 7.4 Dispensing arrangements

Health professionals dispensing opioid pharmacotherapy to patients are an integral part of the treatment team, particularly as frequent contact with patients facilitates the development of good rapport.

### 7.4.1 Communication between prescriber and dispenser

It is important for the prescriber and dispenser to communicate on a regular basis, particularly at the beginning of treatment and during periods of instability and non-adherence. The dispenser should notify the prescriber or treating team when a patient becomes unstable between clinical reviews.

### 7.4.2 Supervised dosing at the drug treatment centre

In most jurisdictions, OST will be dispensed at the site of prescription, allowing regular monitoring of the patient and easy communication between the dispenser and prescriber.

A common mechanism for ensuring adequate documentation is the use of a dosing card by the prescriber and dispenser. An example is given in Appendix F. A dosing card should contain the following information:

- Name and date of birth of the patient (or another identifier to differentiate in the case of identical names)
- A photo may be useful though not always possible
- Type of treatment and dosage – may also be written in words to reduce the chances of misreading
- Route of administration
- Dates between which the prescription is valid
- Dose in milligrams (mg)
- A record of each dose dispensed, signed by the dispenser

In many areas of South and South-East Asia not all of these components may be possible; however, the principle is that sufficient information should be provided to allow confirmation of identity, medication and dose.

### 7.4.3

#### Supervised dosing at an external pharmacy

Dosing at an external dispensing site requires active communication between the prescriber and dispenser. Dispensing at an external site occurs in only a minority of jurisdictions.

A chain of events to ensure safe external dispensing is recommended:

- Contact with the dispenser should be made by the prescriber or allied health professional and patient prior to commencing treatment.
- A record of the dispensing site details should be kept in the patient notes by the prescriber.
- The following should be forwarded to the dispenser
  - Prescription
  - Identifying information (e.g. copy of identity card and photograph)
- It is prudent for the prescriber to verbally confirm the starting dose with the dispenser.
- There are a number of ways to ensure that the prescription forwarded to the external dispensing site is not modified in any way. The original may be given to the patient, peer worker or allied health worker to give directly to the dispensing site **and** a copy faxed or scanned and emailed **or**, if this is not possible, a phone call by the prescriber to confirm dosing instructions.
- The prescriber or treating team should inform the dispensing site of all changes to dosing instructions – contact with the dispensing site should be recorded in the patient’s file.
- Dispensing sites should inform the treating team of any changes to dispensing – contact with the treating team should be recorded in the patient’s file.
- Except in emergencies, dispensers should not dispense opioid pharmacotherapy without a valid prescription. Examples might be a long-term patient who is unable to obtain an appointment for a further prescription prior to expiry of the previous prescription or an unrelated medical emergency.

#### 7.4.4

#### Dispensing in closed settings

Dispensing of opioid pharmacotherapy in closed settings (i.e. prisons, detention centres, boot camps and mandatory treatment centres) has specific issues which are addressed elsewhere.<sup>16,20,21</sup>

OST in closed settings is an important part of an opioid dependence treatment system to ensure continuity of treatment/care as many patients will spend time in jail due to the illicit nature of their activities. Despite this, OST is available in only limited sites across Asia. In general, methadone is preferable to buprenorphine for the treatment of opioid dependence in closed settings as it is more effective and less likely to be diverted.

Detention in closed settings is often unexpected. Dispensing arrangements should commence as soon as practicable. Ideally, custodial arrangements should not interrupt treatment. It is usually more convenient for the patient's dose to be dispensed within the closed setting rather than transporting the patient daily to a drug treatment centre. Only supervised dosing should be provided in closed settings to minimize the risk of diversion and related harm through illicit injecting.

Continuity of treatment (throughcare) should also be ensured after the sentence has been completed and the patient is due to return to the community. Arrangements should be made so that there is minimal interruption of treatment on transfer to the community as the risk of overdose, relapse and risk behaviour is higher in the few weeks immediately after release to the community. There is often a lot of mobility and transfer to different systems resulting in potential disruptions to treatment. Every attempt should be made to ensure continuity of treatment and, where ongoing OST is not possible, the patient should be medically assisted for withdrawal.

The practice of initiation to OST prior to discharge is important in patients who have relapsed earlier and have chronic, refractory opioid dependence. This helps to reduce the potential for overdose and ensures a better clinical outcome

on return to the community. Typically, it is commenced in the final months of detention, allowing enough time to achieve a stable dose prior to discharge. Individuals who are not opioid tolerant need to be carefully inducted to OST to minimize the risk of overdose.

## 7.5 Unsupervised (take-home) dosing

Unsupervised dosing provides greater flexibility to patients and a degree of empowerment through engendered “trust”. Take-home dosing is important in rural areas or where there are logistical difficulties associated with attending a dispensing service daily.

### 7.5.1 Criteria for take-home dosing

Take-home dosing generally refers to methadone substitution therapy only. Take-home doses of buprenorphine are generally not recommended as the risk of the patient injecting their buprenorphine is high. Take-home dosing for those patients on a combination of buprenorphine–naloxone may be more appropriate although there is currently insufficient evidence to support this claim. Patients on supervised buprenorphine-based therapy can be dosed as infrequently as three times a week using double and triple doses. Patients should be clinically stable prior to being given take-home doses. Take-home medication should be identical in dose to supervised doses.

The patient should be assessed for stability before take-home dosing is commenced. Assessment for stability (usually within the previous one to two months) should include the following:

- Current adherence to supervised dosing
- Current adherence to appointments with the treatment team
- Infrequent use of additional illicit opioids or other drugs (may or may not be confirmed with a random urinary drug screen)
- Stable mental health
- Stable accommodation
- Secure area to store medication (particularly if there are children at home)
- Little evidence of concern for diversion or injecting of take-home doses.

It can be difficult to assess whether or not a patient is sufficiently stable for take-home dosing. Consultation for the decision on take-home dosing should be done with the entire treatment team including the dispenser.

Take-home dosing might progress as follows:

- No take-home doses in first two months of treatment
- Assess stability—one take-home dose per week
- Assess stability over one month—two take-home doses per week
- Assess stability over one month—three take-home doses per week
- Assess stability over one month—four take-home doses per week.

It is recommended that a maximum of four take-home doses of methadone be given each week for highly stable patients, meaning that patients will have supervised dosing three times a week.

Take-home dosing is not recommended in the following situations:

- Polysubstance use
- Recent overdoses or presenting in an intoxicated state for dosing
- Unstable psychiatric conditions
- Patient is considered likely to inject take-home doses.

### 7.5.2 Take-home dosing for patients in rural areas

It may be difficult for patients being treated for opioid dependence in rural areas to attend daily supervised dosing. If this is the case, take-home dosing may commence earlier in the course of treatment. As the risk of adverse events on methadone is higher within the first two weeks of treatment, patients should be encouraged to have supervised dosing for at least these first two weeks.

Dosing in the village should be done with the supervision of the local village health volunteer or similar person to ensure adherence, particularly in the initial months of treatment. It is recommended that weekly take-home doses be given in this situation (i.e. six doses maximum) so that patients can be reviewed regularly by the treatment team. Where a patient has been stable for a longer period of time or the village health volunteer or similar person is clinically proficient in providing therapy with methadone, a greater number of take-

home doses may be possible. Village health volunteers or similar persons should be trained in the provision of OST.

## 7.6 Split dosing

Split dosing refers to twice-daily dosing. A small minority of patients may benefit from split dosing. Split dosing is indicated when a patient experiences withdrawal symptoms within 12 hours of administration of the drug, despite being on a high dose of methadone. This may be more common in the third trimester of pregnancy or when a patient is taking other medications which alter the metabolism of methadone. While dispensing split doses, the morning dose is usually supervised while the afternoon dose is consumed at home. In the case where a take-home dose is not safe, both doses should be supervised.

## 7.7 Transferring to another clinician for OST

A transfer may be temporary or permanent. Transfer between clinicians generally requires the consent of all parties or, at the very least, good communication.

Clinical information about the patient should be forwarded to the new prescriber by mail, fax or by hand. The following information should be contained in the referral letter:

- Name, date of birth, address and contact details of the patient
- Photo identification (copy)
- Type and dose of OST
- A brief drug and alcohol history including treatment received
- Other medical or psychiatric problems and medication for these
- Recent progress including adherence and psychosocial issues
- Details of the most recent dose and contact details of the previous dispenser
- Contact details of the prescriber and treatment team.

## 7.8 Termination of treatment

Treatment may be ceased voluntarily or, in a small minority of patients, without consent.

## 7.8.1

### Voluntary cessation of OST

Although methadone and buprenorphine are effective treatments, many patients do not want to remain on therapy for the rest of their lives. Most patients, having achieved a stable dose and stability in their lives, will then gradually want to reduce the dose of OST. Those who eventually reach low-dose therapy may plan to cease completely. Complete cessation is only recommended when the patient is socially engaged with their family or friends, ideally has employment or is engaged in regular extracurricular activities and is not engaging in opioid and, ideally, other drug use. Cessation is usually not recommended in the first 12 months of treatment.

Methadone should be reduced at the following rate:

- Dose >50 mg      maximum of 5 mg/week
- Dose 30–50 mg    maximum of 2.5 mg/week
- Dose <30 mg      maximum of 1–2 mg/week

Patients may experience withdrawal symptoms for a number of weeks after cessation despite very gradual tapering of the dose during the final 5 mg of therapy.

Many patients find buprenorphine easier to reduce than methadone.

Buprenorphine should be reduced at the following rates:

- Dose >8 mg      4 mg/week
- Dose <8 mg      2–4 mg/week
- Dose <2 mg      0.5–1 mg/week

#### 7.8.1.1

##### Transfer from methadone to buprenorphine to complete withdrawal

Patients on methadone therapy can be transferred to buprenorphine during reduction in dose as cessation from buprenorphine may be better tolerated than that from methadone. Transfer may occur when the daily methadone dose is less than 30 mg, though transfer at higher doses (up to 80 mg) has been demonstrated as feasible. The final dose of methadone should be followed by a day free of either methadone or buprenorphine. Buprenorphine should be commenced the following day in accordance with the buprenorphine induction

regimen. Patients should be warned that they may experience moderate to severe withdrawal during transfer, which should settle once the buprenorphine dose is therapeutic. Some patients may not be comfortable even at the maximum dose of buprenorphine following transfer due to the partial agonist nature of buprenorphine. This is more likely to occur in those transferred from high doses of methadone.

Transfer from buprenorphine to methadone for the purpose of withdrawal is not recommended as the severity of withdrawal symptoms from methadone are likely to be greater than those from buprenorphine.

### 7.8.2 Involuntary cessation of OST

It may be decided to discontinue a patient on OST because the patient is making unsatisfactory progress or is putting themselves or others at risk. In this situation, the potential risks to the individual from having their therapy ceased need to be balanced against the potential risks to others (patients and staff) if the patient continues. All reasonable attempts should be made to retain the patient in treatment or transfer the patient to another service that may be more accommodating.

Reasons for involuntary cessation may include:

- Violence, threats or abuse to staff or other patients
- Confirmed drug dealing or other illegal activities around dosing points
- Continued use of dangerous quantities of other central nervous system (CNS) depressant drugs
- Repeated failure to attend for treatment
- Diversion of methadone or buprenorphine
- Trafficking of take-away doses.

Abrupt termination of treatment or dramatic reduction in dosage is rarely warranted and associated with marked deterioration in behaviour, drug use and emotional stability.

## 7.9 Dealing with specific clinical situations

### 7.9.1 Intoxication

Patients intoxicated with sedatives such as alcohol, opioids or benzodiazepines should be assessed clinically before administration of OST.

- Moderately intoxicated patients should be asked to return later in the day when they are not intoxicated or to wait at the dispensing agency or treatment centre until such time as they are alert.
- Mildly intoxicated patients should be assessed prior to dose administration and given a reduced dose (e.g. 50% of the methadone dose).

### 7.9.2 Overdose

Patients on methadone are at higher risk for overdose than those on buprenorphine. The risk of overdose is highest in the first two weeks of treatment. After dose stabilization, those on a higher dose are at less risk of overdose than patients on lower (<60 mg) doses. This is thought to be due to the fact that high-dose methadone increases tolerance to opioids and therefore the threshold for overdose. Overdose is usually associated with the use of other sedatives, particularly benzodiazepines.

Patients on buprenorphine are generally not at risk for overdose except in the case of individuals who use large amounts of benzodiazepines and are not tolerant to the effects of these sedatives.

The treatment of overdose in individuals on opioids including methadone is cardiopulmonary resuscitation (CPR) with naloxone as initial drug therapy and monitoring in hospital. Naloxone has a short duration of action, which can be lengthened by administering it intramuscularly. Failure to rouse the patient following administration of naloxone indicates overdose from another sedative. Respiratory support with oxygen and ventilation may be needed, so patients will have to be transported to a hospital. The effects of buprenorphine are not readily reversed by naloxone. Ventilation is the primary management strategy.

The signs of opioid overdose are:

- Pinpoint pupils
- Peripheral cyanosis (blue tinge to the fingers)
- Respiratory depression (not breathing)

Further information on the management of overdose during OST is given in Appendix B.

### 7.9.3 Missed doses

It is not uncommon for patients to miss supervised doses of methadone or buprenorphine. The reasons may be valid, such as family or employment commitments, or related to continued drug use. It is often difficult to confirm why doses have been missed.

Intermittent missed doses (one to two a month) do not necessarily indicate instability. Patients who regularly miss one or more doses a week should be reviewed by the treating team. If patients are missing doses to use opioids, the dose of methadone or buprenorphine should be increased.

**Table 3.** Management of missed doses during opioid substitution therapy

No. of days missed	Recommended action
1 day	Continue current dose, review at next appointment
2 days	Review by treatment team Continue at current dose
3 days	Review by treatment team Continue current buprenorphine dose Give half methadone dose and resume normal dosing the following day
More than 3 days	Review by treatment team Give half buprenorphine dose and resume normal dosing the following day Give half methadone dose and resume normal dosing the next day Keep under close observation during following few days
If 5 days have been missed, begin new induction	

### 7.9.4 Incorrect dosage administration

Errors commonly occur in the context of a new, inexperienced dispenser unfamiliar with the patient. It is not uncommon for unfamiliar dispensers to

confuse the methadone dose – reading it as millilitres of methadone rather than milligrams. This can result in very high doses of methadone being given.

Incorrectly administered high-dose methadone is not necessarily dangerous in the context of only opioid dependence and current therapy with high dose (>60 mg) methadone. Patients should be monitored for signs of sedation for four hours after the incorrect dose. It is not recommended to induce vomiting.

Incorrect buprenorphine dose administration does not generally require monitoring unless it occurs in the context of polysubstance use with other sedatives such as benzodiazepines. If this is the case, patients should be monitored for four hours after the incorrect dose for signs of intoxication or respiratory depression.

### 7.9.5 Vomited doses

Vomiting of doses, if it occurs, is only relevant to methadone as buprenorphine is sublingually administered. Methadone is rapidly absorbed so vomiting more than 20 minutes after administration probably results in little loss of dose.

**Table 4.** Management of vomited doses during opioid substitution therapy

Time of vomiting	Witnessed?	Action
Vomiting >20 minutes after dose	Witnessed or unwitnessed vomiting	Methadone has probably already been absorbed so no action required
Vomiting <20 minutes after dose	Witnessed vomiting of methadone dose	Re-administer same dose of methadone
	Unwitnessed vomiting of methadone dose	Review patient in 4 hours' time to assess whether or not the patient is experiencing withdrawal  Signs of withdrawal – give normal dose  No signs of withdrawal – no dose, resume the following day

## 7.10 Alternative treatment

Many patients with opioid dependence will have other mental health and psychosocial issues which may benefit from treatment during OST.

In many communities, traditional healers have a role in treating the ill. Family members may take their opioid-dependent relative to a traditional healer to facilitate recovery. Although there is little evidence that traditional healing methods are effective in the treatment of substance use, patients and family members may believe they have a role. In this scenario, it is most important to encourage patients with a serious medical condition, for example, hepatitis or HIV, to seek medical treatment rather than using traditional medicines.

## 7.11 Psychosocial interventions

Psychosocial interventions are most effective when used in combination with OST.

### 7.11.1 Contingency management

Contingency management is a method used to change behaviour by rewarding desirable behaviour. Some techniques may provide negative consequences for undesirable behaviour. In essence, it is a structured system of boundaries agreed upon by patients and the treatment team prior to initiation of treatment.

Contingency management can be administered by any staff with relatively little training. The major elements are as follows:

- Clear definitions of the desirable behaviour such as abstinence from opioids
- Regular monitoring for the presence or absence of the desired behaviour; for example, looking for evidence of fresh injecting sites
- Specified rewards for the desired behaviour such as money, vouchers, take-home methadone doses, lottery tickets
- Positive personal feedback from staff for the desired behaviour.

Contingency management can be related to any desirable behaviour that has specific outcomes with a potential for reward.

### 7.11.2 Cognitive–behavioural therapy

CBT should be administered by trained clinical psychologists. CBT for opioid dependence focuses on the notion that behaviours are a function of beliefs. For example, substance dependence is a learned behaviour capable of being modified through correcting distorted belief patterns.

The “cognitive” component of CBT aims to change distorted, negative thinking styles and rationales for substance use. It follows that once a patient has “reprogrammed” their thinking around drug use, they will make better decisions about their use, resulting in reduced use and harm. An example is being able to identify, and hence avoid, high-risk situations which might lead to relapse.

The “behavioural” component of CBT aims to reinforce positive behaviour associated with good outcomes. Contingency management is an example.

### 7.11.2 Self-help groups

These groups are voluntary, run by peers, generally small and meet regularly. Patients may find that self-help groups provide emotional support and a sense that they are not alone in the struggle with opioid dependence. Although there is little evidence that self-help groups such as Narcotics or Methadone Anonymous are effective in reducing drug use, they are inexpensive and simple to provide. Peer educators may facilitate a self-help group as part of their role.

### 7.11.3 Brief interventions

Brief interventions should always be a part of therapy and are discussed in Section 6.3.1.1 (p. 18). Brief interventions can cover any topic of relevance and importance to the patient, and are best done in the context of a strong, respectful professional relationship. There are a number of different schemata for brief interventions. One example is that of the acronym FRAMES.<sup>22,23</sup> In this case, it applies to substance use.

Feedback	Personal <b>feedback</b> about the risks associated with continued substance use based on the current pattern of use, problem indicators and health status
Responsibility	Emphasis on the individual's personal <b>responsibility</b> and choice to reduce or seek treatment for substance use
Advice	Clear <b>advice</b> about the importance of changing current substance use patterns
Menu	A <b>menu</b> of alternative change options. This emphasizes the individual's choice, and allows them to choose the approach best suited to their own situation.
Empathy	<b>Empathy</b> from the person providing the intervention is an important determinant of patient motivation and change. A warm, reflective and understanding brief intervention is more effective than an aggressive, confrontational or coercive style.
Self-efficacy	<b>Self-efficacy</b> involves instilling optimism in the patient that his or her chosen goals can be achieved. It is in this step, in particular, that motivation-enhancing techniques are used to encourage patients to change.

## 7.12 Peer programmes

Peers are well accepted by other peers within the drug-using community. For this reason, peer programmes including peer education and peer group work can be helpful in building strong relationships with opioid-dependent individuals. Peer education officers may not have formal health qualifications and are thus inexpensive for a clinic to employ.

Peer programmes are based on the concept that individuals with good interpersonal skills, who are interested in health-related learning, can be trained to provide information and education to their drug-using counterparts. Training is generally step-wise, and builds knowledge over time.

The role of a peer educator is

- To develop relationships with drug users in the community

- To provide health information to drug users in the community
- To provide information and facilitate access to harm reduction interventions
- To provide referrals and link drug users to local health services such as the drug treatment centre.

To maintain a strong ethical framework, peer educators should

- Provide accurate, unbiased information to drug users
- Provide drug users with information in a respectful, confidential manner
- Provide information which is helpful to drug users in maintaining their health
- Maintain confidentiality except with the treatment team.

Peer educators have some limitations:

- Peer educators are not nurses or doctors and cannot be expected to know everything. Peer educators are not able to provide treatment.
- Drug use occurs at all hours and on all days of the year. Peer educators cannot be expected to work all hours as this may lead to burnout and diminished capacity.
- Inaccurate information can be counterproductive and sometimes dangerous. Therefore, peer educators should only give information relating to their specific areas of training.

If in doubt, peer educators should refer their patients to somebody more knowledgeable.

## 7.13 Management of polysubstance use (benzodiazepines, alcohol, ATS)

In much of South and South-East Asia, it is increasingly becoming common for opioid-dependent patients to engage in the harmful use of other substances. The most common in the Region, depending on the country, are benzodiazepines, ATS and alcohol. Cannabis use is also ubiquitous.

Polysubstance use, also known as polydrug use or multiple drug use, includes the use of “cocktails” of illicit and licit drugs combined to obtain increased effect.

Polysubstance use should be managed with the following principles:

- Prescribe only one substance from one class of medications, i.e. if an individual takes codeine and heroin, replace with only methadone or buprenorphine. If an individual takes illicit alprazolam, midazolam and/or diazepam, treat only with regulated diazepam.
- Substitute long-acting in place of short-acting medications, i.e. if an individual is taking alprazolam (short-acting benzodiazepine) then replace with diazepam which is long-acting.
- Consolidate the use of sedatives, aiming at the use of only one medication with sedative properties to minimize the risk of overdose.

### 7.13.1 Benzodiazepine dependence

Benzodiazepine use is common in opioid-dependent individuals to relieve withdrawal symptoms and increase the effects of opioids, which are usually more expensive. The type of benzodiazepine used depends on the context and current trends within drug-using populations. Generally, short-acting benzodiazepines such as midazolam, alprazolam and temazepam are more likely to be used in a harmful way. Injectable forms of benzodiazepines such as midazolam are also increasingly being used in a harmful way in some countries.

Opioid-dependent patients engaging in harmful benzodiazepine use should be commenced on 20 mg of methadone. The dose is increased by 5–10 mg every 5 days, with frequent review by the treatment team.

Patients currently engaging in harmful benzodiazepine use should be cautiously inducted on methadone. These patients are at a higher risk for overdose or death, particularly in the first two weeks of treatment.

Particular caution should be used when a benzodiazepine-dependent patient on OST has missed doses as such patients may be at high risk for overdose. Patients should be reviewed daily by the treatment team on reinstatement of treatment.

#### 7.13.1.1 Treatment of benzodiazepine dependence

It is difficult to treat benzodiazepine dependence or harmful use in settings where benzodiazepines are freely available over the counter at pharmacies. In

those jurisdictions where benzodiazepines are regulated through authorized prescription systems it is likely that benzodiazepines will still be relatively easily available as street drugs.

The following principles should be followed in the context of treatment for benzodiazepine dependence:

- Long-acting benzodiazepines (e.g. diazepam) are preferable to short-acting ones (e.g. alprazolam).
- Injectable benzodiazepines should not be prescribed.
- Administration should, where possible, be directly observed.
- It is not advised to reduce the dose of methadone or buprenorphine during benzodiazepine reduction.
- Do not abruptly cease patients on high-dose benzodiazepines due to the risk of seizures.
- The longer and slower the detoxification regimen, the more likely patients are of being successful.

With this in mind and emphasizing caution, **diazepam-assisted withdrawal** includes the following:

- Convert patients to “diazepam equivalents”. An equivalence table is given in Appendix H.
- Reduce the prescribed dose of diazepam by 2.5–5 mg per week to the lowest tolerated dose (the dose of OST may need to be increased).
- If facilities are available, a short inpatient stay at a drug rehabilitation centre should be utilized to assist in withdrawal from benzodiazepines. For benzodiazepine withdrawal on an outpatient basis, it is important to reduce the dose very gradually to prevent relapse and disengagement with treatment.
- The use of sedating antipsychotics or gabapentin is currently not supported by evidence.

Symptoms of benzodiazepine withdrawal may persist for weeks after complete cessation. Major withdrawal symptoms are:

- Insomnia
- Irritability and anger
- Anxiety

- Problems with short-term memory
- Depersonalization/derealization
- Seizures (rare if reduction is gradual)
- Muscle twitches, jerks, tinnitus, hallucinations, tingling, numbness and altered sensation.<sup>24</sup>

### 7.13.2

#### Amphetamine dependence

Since 2000, amphetamine use has increased markedly, particularly in South and South-East Asia. The most common type of ATS is methamphetamine also known as *yaba* or *yama*. Injecting of methamphetamine has also been noted. Use of Ecstasy is not uncommon, though injecting is rare.

The most common pattern of methamphetamine use is bingeing for periods followed by periods of abstinence. Each lasts a few days. However, amphetamine dependence (daily use) is not infrequent.

Opioid-dependent patients are likely to have used amphetamines over time and during treatment for opioid dependence, depending on the setting.

Clinical symptoms and signs of amphetamine intoxication are:

- Rapid speech
- Agitation and anxiety
- Insomnia
- Elevated mood and confidence
- Psychotic symptoms such as delusions, e.g. paranoia
- Dilated pupils
- Sweating
- Tachycardia (racing pulse)

Clinical symptoms and signs of withdrawal include:

- Depressed mood
- Fatigue
- Sedation
- Irritability and anxiety
- Craving and drug-seeking behaviour

### 7.13.2.1

#### Management of amphetamine dependence

There is little evidence of effective treatment for amphetamine dependence and even less for harmful use. Psychosocial interventions such as relapse prevention may be helpful. Pharmacological treatment should aim to relieve symptoms. The treatment team should focus on treating other underlying dependencies as well as mental health issues associated with amphetamine use including depression and suicidality.<sup>25</sup>

Non-pharmacological management of amphetamine dependence includes relaxation and sleep advice, providing a safe environment, contingency management counselling and the provision of family and other support. Inpatient withdrawal is usually not required unless there are psychiatric complications, a previous history of complicated withdrawal, absence of social support and polydrug dependence.

In cases of complicated ATS intoxication, management should consist of correcting fluid and electrolyte imbalance, monitoring the blood pressure and ECG, sedation for extreme agitation and monitoring for hypo- or hyperthermia.

### 7.13.3

#### Alcohol dependence

Although the use of alcohol varies widely across South and South-East Asia, it remains an extremely common form of harmful substance use and dependence, particularly among men. Harmful alcohol use (binge drinking) is more common than alcohol dependence (drinking every day). Younger patients are more likely to engage in harmful alcohol use. Dependence is equally common across ages.

Reducing alcohol use in the context of opioid dependence is important for two major reasons:

- Many IDUs have hepatitis B or C or both and alcohol use will increase progression to chronic liver disease and cirrhosis.
- Alcohol is a sedative which can increase the likelihood of overdose in polysubstance users, particularly in patients with chronic liver disease.

Clinical symptoms and signs of alcohol intoxication are commonly known and include the following:

- Ataxia (poor coordination)
- Slurred speech
- Sedation

Patients with alcohol dependence may have the following clinical syndromes:

- Malnutrition
- Peripheral stigmata of chronic liver disease such as spider naevi and peripheral oedema
- A tender or firm liver edge
- Ascites
- Where pathology services are available, biochemical evidence of anaemia, a low platelet count and abnormal liver function tests may also be present.

Clinical symptoms and signs of alcohol withdrawal include:

- Sweating
- Diarrhoea
- Tremor
- Confusion
- In severe cases, seizures, usually in the first 24–48 hours after cessation.

### 7.13.3.1

#### Treatment of alcohol dependence

A useful tool to screen for problematic alcohol use is the Alcohol Use Disorders Identification Test (AUDIT), which is reliable across cultures and endorsed by WHO.<sup>26</sup> More information on its use can be obtained from *AUDIT – the alcohol use disorders identification test: guidelines for use in primary care*.<sup>27</sup>

Opioid-dependent individuals engaging in problematic alcohol use should be treated. Treatment is generally divided into two parts – management of withdrawal and prevention of relapse. Most individuals will need to aim for abstinence, as there is little evidence that individuals with long-term problematic alcohol use are able to engage in controlled drinking.

Treatment of withdrawal should be guided by trained clinicians and cover the following principles:

- Most individuals will not need medicated withdrawal regimens.
- Diazepam-assisted withdrawal is the most common form of treatment to relieve symptoms and prevent seizures.
  - Diazepam is prescribed for four days after cessation of alcohol use and, in individuals on OST, it is safest done in the inpatient setting.
  - Dosing should be “symptom triggered”, i.e. taking only as much medication as is needed to control symptoms.
  - The maximum dose of diazepam per day should be guided by the severity of alcohol dependence. It is generally between 40 and 80 mg.
  - Diazepam should be stopped on day 5 post cessation of alcohol.
- All individuals with problematic alcohol use should be encouraged to eat a normal, balanced diet. Thiamine supplements are recommended in chronic alcohol-dependent individuals.

Prevention of relapse should be guided by trained clinicians. The most important predictor of success is retention in treatment – **longer retention results in a better outcome, no matter the method of treatment.** The following methods of treatment are effective:

- Psychosocial interventions such as CBT, motivational interviewing, self-help groups and counselling
- Anticraving medication can reduce cravings for alcohol and prolong abstinence.
  - Acamprosate (tablet) 666 mg three times daily is recommended for individuals on OST.
  - Naltrexone (tablet) 50 mg daily cannot be used in patients using opioids as it will cause acute withdrawal, though it is effective in reducing relapse to alcohol in individuals not using opioids.

## 7.14 Managing patients with special needs

### 7.14.1 HIV and opioid dependence

Sharing injecting equipment is a common mode of HIV transmission across South and South-East Asia. All IDUs should be provided, where possible, with access to new, sterile injecting equipment.<sup>28</sup> It is a key function of peer educators to provide people who inject with information about harm reduction and other methods of reducing the risk of acquiring HIV.<sup>12</sup> Similarly, HIV-positive individuals should be counselled on the importance of injecting using their own equipment and ensuring its safe disposal.

#### 7.14.1.1

##### Offering HIV testing and counselling to persons with opioid dependence

HIV testing and counselling should be offered to all patients with opioid dependence, as they are at high risk for acquiring the virus. Normal clinical activity for prescribers and the drug treatment team should include developing a relationship with the local HIV testing and counselling service to allow easy referral.

#### 7.14.1.2

##### Stabilizing opioid-dependent persons on OST before initiating antiretroviral therapy

Optimal HIV treatment is dependent on very good adherence to antiretroviral therapy (ART). Adherence to ART in drug-using populations can be improved by first stabilizing such patients on OST for the treatment of opioid dependence. The stabilization period prior to ART initiation may be around two months, although there is little evidence to support a fixed period of stabilization prior to ART.

#### 7.14.1.3

##### Counselling patients regarding interactions between OST and ART

Methadone interacts with a number of antiretroviral (ARV) medications which may reduce the effectiveness of some ARVs and increase side-effects from others.

ARVs can alter the levels of methadone in the blood so careful monitoring of symptoms is required during commencement of ART in patients on methadone. Dose adjustment may be necessary.

Interactions between buprenorphine and ARVs do occur but are less common and only with some of the newer ARVs (protease inhibitors). Dose adjustment of buprenorphine is often not required.

A table on the interactions of ARVs with methadone and buprenorphine can be found in Appendix E. Further information on care and treatment of HIV in IDUs can be found elsewhere.<sup>29-31</sup>

## 7.14.2 Tuberculosis and opioid dependence

### 7.14.2.1 Screening opioid-dependent persons for TB

TB is not uncommon among drug users because of the low socioeconomic status, and poor general health and nutrition of many opioid-dependent patients. Many are also HIV-infected, which further compromises their nutritional and health status.

### 7.14.2.2 Stabilizing opioid-dependent persons on OST to improve adherence to anti-TB medication

Patients with opioid dependence may adhere better to complex medication regimens such as antituberculosis treatment (ATT) once their drug use has been stabilized with OST. This also helps to improve retention in treatment. Patients taking supervised or directly observed OST and needing treatment for TB should be given DOT, preferably together with their OST.

### 7.14.2.3 Counselling patients regarding interactions between OST and ATT

Several medications used for ATT, in particular rifampicin, can interact with methadone. A full discussion of these interactions is given in Appendix E, and on the prevention, treatment and care of TB in IDUs in other guidance documents.<sup>32</sup>

### 7.14.3 Managing pain during OST

#### 7.14.3.1 Management of patients with acute pain

Patients having acute pain while on methadone or buprenorphine should be treated with simple non-opioid analgesics such as paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs (NSAIDs), especially when there is an inflammatory component to the pain. A short-acting opioid analgesic is often required concurrently.

The management of severe acute pain in patients on methadone requiring hospitalization should be similar to normal patient management (i.e. parenteral opioids), except that higher doses of the treating opioid may often be required due to opioid tolerance. Where possible, the methadone dose should be continued during the hospital stay, with additional opioid analgesics as necessary.

Patients requiring hospitalization while on buprenorphine-based therapy should be treated where possible with non-opioid simple analgesia as the effect of other opioids will be attenuated (buprenorphine blocks the effects). Those in severe pain that cannot be controlled in this fashion will need specialized anaesthetic review, and regional anaesthesia (nerve blocks) or ketamine infusion.

#### 7.14.3.2 Management of patients with chronic pain

Methadone (or another long-acting opioid) is preferable to buprenorphine for treating chronic pain as it has greater analgesic properties. In patients with chronic pain, the origin of the pain should be clinically investigated prior to treatment with methadone. Referral to a specialist in the necessary field is recommended, and a second opinion sought where the management plan is not clear.

Patients with chronic pain often have significant psychosocial and mental health issues, which should be managed during treatment. Depression, in particular, is common.

Patients with chronic pain can be co-managed by the prescriber and the clinical specialist from the relevant field.

#### 7.14.4

#### Management of patients with psychiatric co-morbidity

IDUs and those who are opioid dependent commonly have psychiatric co-morbidities. It is often difficult to tell whether there is a causal relationship between the substance use and the mental health issue. Patients may need to be referred to a psychiatrist or a health professional with a mental health background.

##### 7.14.4.1

##### Depression in opioid dependence

Depression and anxiety are the two most common forms of mental illness associated with substance use. Anxiety may be related to withdrawal symptoms and may subside with OST. Depression can be more sinister. Patients should be screened for depression as suicide is not uncommon in risk groups such as substance users. Patients diagnosed with depression should be treated pharmacologically where possible – most antidepressants are off patent and increasingly accessible. Pharmacological treatment for depression takes around two to six weeks to have an initial effect. Treatment should be continued for at least six months for a first episode of depression.

##### 7.14.4.2

##### Manic episodes due to ATS use

It is important to exclude drug use as a cause of manic or hypomanic episodes in patients with a history of depression. Drug-induced mania is not uncommon following stimulant use such as ATS. Mania or hypomania not associated with drug use should lead to a consideration of bipolar disorder.

#### 7.14.4.3

#### Psychotic episodes due to drug use

Psychoses can be primary, or associated with drug use. ATS are the most common psychoactive substances to induce psychosis. Opioids generally have an antipsychotic effect. Opioid-dependent patients who have had psychotic episodes should be formally evaluated to exclude drug use as a cause of the psychosis. Drug-induced psychosis does not normally need medication to resolve. Patients having psychosis without a recent history of stimulant or hallucinogen use may have a primary psychosis such as schizophrenia. Primary psychoses are difficult to manage and patients should be referred to a mental health-specific service.

### 7.15

#### Opioid dependence and pregnancy

The demographics of opioid dependence show that opioid-dependent females tend to be in the fertile years, which means that pregnancy is not uncommon among female patients. All attempts should be made to engage and retain in treatment pregnant women in the early stages of pregnancy to optimize antenatal care. This includes screening for other substance use and mental health issues, as well as for bloodborne viruses. Folate supplementation and psychosocial support should also be provided.

Opioid withdrawal is generally not recommended during pregnancy due to poorer pregnancy outcomes.<sup>33</sup> Where possible, pregnant women should be recommended substitution therapy using methadone as it is associated with the most favourable outcomes. Although buprenorphine has been used in pregnancy with good outcomes, safety data are limited. In the case that a patient discovers she is pregnant while currently on buprenorphine substitution therapy and is unwilling to commence methadone, the patient should continue buprenorphine after receiving counselling about the limited data on risk. As in most cases, pregnancies in this population are not planned. Family planning and birth control including effective contraception need to be offered to women who enter treatment for opioid dependence.

### 7.15.1

#### Methadone dose increase during pregnancy

As pregnancy proceeds and fluid retention increases the volume of distribution, the dose of methadone may need to be increased. For this reason and due to other metabolic changes, methadone may have to be increased by 5–10 mg or occasionally more in the latter half of pregnancy. Split dosing (twice daily) may also be required in some cases. Post partum, the dose may need to be reduced.

### 7.15.2

#### Breastfeeding and methadone

Breastfeeding while on methadone is not associated with adverse outcomes and should be recommended to all women.

### 7.15.3

#### Monitoring newborn infants for signs of neonatal abstinence syndrome

Neonatal abstinence syndrome (NAS) is an opioid withdrawal syndrome not uncommonly experienced by the newborn infant following birth where the mother is opioid dependent. Withdrawal generally commences within 48 hours of delivery, though it may be delayed in the context of polysubstance dependence, particularly with other sedatives such as benzodiazepines.

Not all newly born infants will suffer from NAS and although it is more likely to develop in infants of mothers with a higher level of opioid dependence, this is not necessarily the case.

Infants should be kept with their mothers where possible to encourage breastfeeding. A validated scoring chart is recommended to monitor progress, particularly in the context where the substance use history is unclear or maternal opioid or benzodiazepine dependence is present.<sup>34</sup> For this and other detailed management, *see* Appendix G.

**Table 5.** Signs of the neonatal abstinence syndrome<sup>34</sup>

Common signs	Less common signs
Irritability and sleep disturbances	Yawning
Sneezing	Vomiting
Fist sucking	Increased mucus production
Shrill cry	Increased response to sound
Watery stools	Convulsions (rare)
General hyperactivity	
Ineffectual sucking	
Poor weight gain	
Dislike of bright lights	
Tremors	
Increased respiratory rate	

Source: Henry-Edwards et al. (2003)<sup>35</sup>

## 7.16 Opioid dependence in children and adolescents

Early development of harmful opioid or other drug use is associated with poorer long-term outcomes for a variety of reasons, including permanent changes to brain development and the impact on educational, employment and social opportunities. Adolescents engaging in substance use are more likely to have high-risk, novelty-seeking traits and have high rates of psychiatric co-morbidity.

Adolescent-oriented services should cater to the needs of young people. Adolescent assessment should be comprehensive and include the family where possible. Indeed, many adolescents present with their concerned families. Adolescents are more likely to be attracted to a service other adolescents attend. Social networking is important to adolescents so peer groups of adolescents can increase the likelihood of young people continuing to attend a service. The need for social networking should be balanced against the risks of developing unhelpful relationships with other individuals also engaging in high-risk activities.

Treatment for adolescents should include a combination of psychosocial and pharmacological methods. Many adolescents will be in the midst of

interpersonal difficulties relating to their family and may benefit from family therapy, as parental detachment is associated with poorer outcomes. Therapy should aim at long-term success.

Adolescents unsuccessful at withdrawal or in residential programmes should be considered for OST. Buprenorphine is preferred in this age group as it allows greater flexibility in therapeutic options (easier withdrawal or conversion to methadone). Adolescents may also benefit to a greater extent than adults from naltrexone as a post-withdrawal relapse prevention therapy.



# 8

## MANAGEMENT OF OPIOID WITHDRAWAL

Detoxification from opioids using a prescribed withdrawal regimen may be useful in a number of situations, although substitution therapy is more effective and preferable in most situations.

**All forms of detoxification as treatment for opioid dependence have high relapse rates.**

Opioid withdrawal should be considered in the following situations:

- Young users or those with a short history of opioid use presenting to a treatment service for the first time
- Highly motivated individuals with strong social support
- Insignificant other drug use
- Patient request
- As a mechanism to engage a patient in treatment
- In closed settings at entry where substitution therapy is not available.

Withdrawal from opioids is not recommended in pregnancy. Where available, patients should be encouraged to commence methadone. Both intake and withdrawal have fetal effects. Withdrawal effects are considered more serious.<sup>33</sup>

### 8.1 Supported outpatient withdrawal

Opioid withdrawal can be community (home)-based outpatient or inpatient (hospital or residential drug treatment).

Outpatient detoxification is preferable to inpatient detoxification as it is cheaper

and the outcomes are similar. Inpatient withdrawal is recommended in the following circumstances:

- Polysubstance use
- Psychiatric co-morbidity
- Poor social support
- Previous unsuccessful outpatient withdrawals
- Patient preference.

## 8.2 Opioid-based withdrawal regimens

Opioid-based withdrawal regimens are better tolerated and include methadone and buprenorphine, among others. If methadone or buprenorphine is available, these are preferred to other prescribed opioids. Buprenorphine is generally better tolerated than methadone for withdrawal and should be preferred where available.

### 8.2.1 Clinical features of opioid withdrawal

Opiate receptors are present in most parts of the body and so withdrawal from opioids affects most systems. Physical symptoms and signs of opioid withdrawal generally appear after 6–24 hours and peak 36–72 hours after the last dose of heroin or morphine-related opioids. Psychological features continue for weeks and sometimes months afterwards. Neurobiological changes to the brain resulting from long-term opioid dependence may persist for even longer, making these individuals always at risk for relapse even in the face of long-term abstinence.

**Table 6.** Clinical features of opioid withdrawal

	System affected	Clinical features
Physical features	General	Feeling hot and cold, yawning
	Eyes and nose	Dilated pupils, runny nose
	Skin	Sweating, piloerection (goosebumps)
	Cardiovascular	Tachycardia, increased blood pressure
	Gastrointestinal	Nausea, vomiting and diarrhoea, abdominal cramps
	Musculoskeletal	Muscular cramps, backache, joint pain
Psychological features	Central nervous system	Anxiety and irritability Depressed mood Insomnia Craving for opioids

Medicated opioid withdrawal attempts to reduce the intensity of these symptoms. Medication does not relieve symptoms completely, and patients should be warned of this. Despite the severity of withdrawal symptoms, opioid withdrawal is rarely life-threatening.

### 8.2.2 OST for those who relapse

Failed attempts are commonly a result of inadequate symptom control and subsequent relapse to illicit opioid use. Patients relapsing during detoxification are likely to fail a subsequent detoxification attempt and should be counselled to commence OST, which can be done at any time during withdrawal.

If OST is not available, patients may benefit from detoxification in an extended-length inpatient programme such as a therapeutic community or inpatient drug treatment centre.

### 8.2.3 Post-withdrawal relapse prevention strategies

Structured post-withdrawal programmes aim to keep patients engaged in the treatment process and focus on avoiding relapse. Psychosocial interventions and support groups may be of help. Ultimately, stable employment, accommodation and family circumstances provide the best bulwark against relapse.

## 8.3 Opioid withdrawal using buprenorphine

The decision to commence buprenorphine for withdrawal should be made after thorough assessment and patient education. Dosing should be directly observed (supervised). As in buprenorphine substitution therapy, no illicit opioids should be consumed within six hours of the first dose, and no methadone within 24 hours.

There is no optimal length of withdrawal regimen, though 10–14 days is recommended. Longer regimens may reduce symptoms, but may also be associated with rebound symptoms after cessation.

### 8.3.1 Buprenorphine dosing

The initial dose sequence and rate of withdrawal should be based on:

- Previous experience of opioid withdrawal
- Current level of opioid use
- Degree of psychosocial support.

The principle is to rapidly increase the buprenorphine dose to a level that completely relieves symptoms, then taper to zero over a period of 7–10 days. A suggested regimen is given in table 6.

**Table 7.** Suggested buprenorphine-assisted outpatient withdrawal regimen

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14*
Dose (mg)	4	8	12–16	12–16	12	10	8	6	4	4	2	2	1	0.5

\* Cease after day 14

Inpatient withdrawal regimens are generally guided by the length of stay, but can be shortened with lower dosing than outpatient withdrawal. Dosing can also be symptom triggered. It is recommended that patients remain in the residential setting for several days after completion of the withdrawal regimen.

**Table 8.** Suggested buprenorphine-assisted inpatient withdrawal regimen

Day	1	2	3	4	5	6	7
Regular dose (mg) (morning)	4	4	4	2	2, as needed	0	0
As needed dose (mg) (evening)	2–4	2–4	2	2	0	0	

### 8.3.2 Persistence of withdrawal symptoms

Most individuals will experience symptoms of opioid withdrawal during this regimen and for several days to weeks afterwards. Some symptoms can be relieved by non-opioid withdrawal medication (*see* Section 8.6) used in combination with buprenorphine and following cessation of buprenorphine, but this increases the complexity of the withdrawal.

## 8.4 Opioid withdrawal using methadone

Methadone is used where buprenorphine-based therapy is not available or where requested by the patient. Methadone-assisted opioid detoxification regimens are generally longer than those with buprenorphine and withdrawal symptoms are more intense.

### 8.4.1 Methadone dosing

Methadone dosing should be flexible. The initial dose sequence and rate of withdrawal should be based on:

- Previous experience of opioid withdrawal
- Current level of opioid use
- Degree of psychosocial support.

As with buprenorphine, the principle is to commence treatment, then increase the dose of methadone to a level that reduces symptoms. The dose is then reduced gradually to zero over 10–14 days.

**Table 9.** Suggested methadone-assisted outpatient withdrawal regimen

Day 1	Days 2-4	Days 5-14
20–30 mg	20–30 mg	Reduce by 2.5–5 mg a day*

\*Hold dose at same level for 2 days if discomfort unmanageable

Like buprenorphine, inpatient regimens can be shorter and of a lower peak dose. The minimum length of inpatient withdrawal should be 5–7 days of methadone followed by several days without methadone prior to discharge to prevent relapse. Non-opioid medication should be used to control withdrawal symptoms during inpatient methadone detoxification.

### 8.4.2 Persistence of withdrawal symptoms

Most individuals will experience symptoms of opioid withdrawal during this regimen and for a number of weeks afterwards with reduced intensity. Some symptoms can be relieved by non-opioid withdrawal medication (*see*

Section 8.6) used in combination with methadone and following cessation of methadone but this increases the complexity of the withdrawal.

## 8.5 Withdrawal using other opioids

Buprenorphine and methadone are not available in many parts of South and South-East Asia, particularly in rural areas. Pharmaceutical opioids can be used to provide medicated opioid withdrawal though they are less preferable. Codeine phosphate and (dextro)propoxyphene are the most commonly used medications though morphine has also been used.

### 8.5.1 (Dextro)propoxyphene and codeine detoxification regimens

These regimens should be supported with non-opioid medication for symptomatic relief. (Dextro)propoxyphene is a long-acting, full opioid agonist used for medical analgesia. It is also a common street opioid in some parts of South and South-East Asia. In the medical setting, dosing is every six hours, though in a withdrawal regimen, dosing can be two to three times daily. A combination of non-opioid medication to relieve symptoms is recommended in conjunction to reduce the dose of (dextro)propoxyphene and control withdrawal symptoms.

A similar approach should be taken for codeine, which is also used in medical analgesia but has a shorter duration of action. Codeine dependence is a common form of pharmaceutical opioid dependence globally. For medical analgesia, codeine is given every 4–6 hours, though in the setting of opioid withdrawal treatment it can be given 3–4 times daily. Non-opioid medication should be used in conjunction to reduce symptoms during withdrawal.

#### 8.5.1.1 (Dextro)propoxyphene and codeine dosing

Dosing of both these medications should be flexible. The initial and peak dose of (dextro)propoxyphene should be determined by the level of opioid dependence. Fixed-dose regimens may not be as effective as variable-dose

regimens as (dextro)propoxyphene has a number of active metabolites. Patients should be reviewed daily.

**Table 10.** Suggested (dextro)propoxyphene-assisted outpatient withdrawal regimen

Day	1	2	3	4	5	6	7	8
Total daily dose (mg)(variable-dose regimen)	300–600	300–600	200–600	100–500	0–400	0–300	0–200	0–100
Total daily dose (mg) (fixed-dose regimen)	800	600	400	200	0	–	–	–
Frequency of divided doses (per day)	3	3	2–3	1–3	2–3	2–3	1–3	1–3

The initial and peak dose of codeine should be determined by the level of opioid dependence. Patients should be reviewed daily.

**Table 11.** Suggested codeine-assisted outpatient withdrawal regimen

Day	1	2	3	4	5	6	7	8	9	10
Total daily dose (mg)	180–240	180–240	120–240	60–210	0–180	0–150	0–120	0–90	0–60	0–30
Frequency of divided doses (per day)	3–4	3–4	3–4	3–4	3–4	3–4	2–4	2–3	1–3	1–2

## 8.5.2

### Tincture of opium

Tincture of opium is used in some parts of South and South-East Asia and is a preparation of opium in alcohol and water. It should not be confused with camphorated tincture of opium (paregoric). Paregoric is a weaker mixture of morphine, benzoate, camphor and anise oil.

Tincture of opium is used as a treatment for opioid withdrawal in some parts of South and South-East Asia. Emerging studies have found it inferior to methadone.<sup>36</sup> At present, there is insufficient evidence to recommend it as a detoxification regimen in preference to the above regimens.

## 8.6 Non-opioid based withdrawal

Non-opioid based withdrawal regimens are recommended where opioid-assisted withdrawal is not available/impracticable, or in the case of patient preference. A combination of medications is used, with primary symptom relief being provided by clonidine, a centrally acting alpha<sub>2</sub>-adrenergic agonist used medically for the treatment of hypertension. Lofexidine has fewer hypotensive side-effects and can be used in place of clonidine, though it is less commonly available.

### 8.6.1

#### Clonidine-based regimens and blood pressure

Blood pressure and heart rate should be measured prior to commencement. To avoid syncope, clonidine should not be used in those with a systolic blood pressure <90 mmHg or pulse rate <50 bpm. Individuals should be counselled to maintain adequate hydration throughout the detoxification process.

A test dose of 75 µg of clonidine is recommended prior to commencement. Lying and standing blood pressure should be measured after 30 minutes. Individuals having a systolic blood pressure <90 mmHg or experiencing significant symptoms such as dizziness following this dose should not be commenced on treatment.

Treatment is titrated against blood pressure and body weight. Five days is usually sufficient, though regimens of up to 14 days have been described.

**Table 12.** Suggested clonidine-assisted inpatient opioid withdrawal regimen

Day	1	2	3	4	5
Total daily dose (µg/kg)	10–17	10–17	9	6	As needed
Frequency of divided doses	Dose four times daily on days 1–4				As needed

When used in the context of outpatient detoxification, clonidine dosing should be less frequent as antihypertensive side-effects cannot be monitored. Patients should be reviewed daily, and only a single day's medication dispensed at one time.

**Table 13.** Suggested clonidine-assisted outpatient opioid withdrawal regimen

Time of dose	Day 1	Day 2	Day 3	Day 4	Day 5
Morning ( $\mu\text{g}$ )	150	150–300	150–300	75	75
Lunchtime ( $\mu\text{g}$ )	150	150–300	150–300	75	–
Evening ( $\mu\text{g}$ )	150	150–300	150–300	75	75

### 8.6.1.1

#### Medications for symptomatic relief during clonidine-based withdrawal

Essentially, symptoms should be treated as necessary. Medications providing symptomatic relief can usually be stopped at the same time as the clonidine-based regimen is completed, though they may be continued on an as-needed basis. Patients should be reviewed daily to allow titration of medication for relief of symptoms.

**Table 14.** Non-opioid medication to reduce symptoms of opioid withdrawal on an as-needed basis

Symptom	Suggested medication	Suggested dosing schedule
Nausea and vomiting	Metoclopramide Prochlorperazine	10 mg orally every 6 hours 5 mg orally every 6–8 hours
Muscle aches	Paracetamol *(acetaminophen)  Ibuprofen*	1 g every 4–6 hours (max. 4 g/day)  400 mg every 6–8 hours (max. 1.2 g/day)
Muscle cramps	Quinine	300 mg twice daily
Abdominal cramps	Hyoscine	20 mg every 6 hours
Diarrhoea	Loperamide  Diphenoxylate/ atropine	4 mg then 2 mg after each stool (max. 16 mg/day)  5 mg/50 $\mu\text{g}$ every 6–8 hours reducing as diarrhoea is controlled

\* Ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs) can be taken in combination with paracetamol.

## 8.7 Post-withdrawal therapies

Following cessation of physical withdrawal symptoms, the risk of relapse will remain high for an extended period of time, particularly if a patient's psychosocial situation is not stable. Post-withdrawal therapies seek continued engagement with the patient to develop techniques helpful in preventing relapse. Pharmacological assistance with the opioid antagonist naltrexone may also be of benefit.

### 8.7.1 Psychosocial interventions

Patients should be encouraged to continue psychosocial interventions. Retention in treatment is the most important factor in achieving effective outcomes for psychosocial interventions. Patients are more likely to continue psychosocial interventions if they enjoy them. For this reason, patients should be encouraged to engage in a number of psychosocial treatments over time in order to find those that are appropriate for their needs. Examples of psychosocial interventions include:

- Counselling, including individual, group and family therapies
- Peer support groups (self-help groups)
- CBT.

Patients should be encouraged to seek employment or engage in volunteer work as a replacement activity in order to boost self-efficacy and reduce the risk of relapse.

### 8.7.2 Naltrexone therapy in addition to psychosocial interventions

Highly motivated individuals may benefit from naltrexone therapy. Naltrexone is an opioid antagonist which reverses and inhibits the effects of opioids. Naltrexone is effective for relapse prevention in alcohol dependence though it has also been used with mixed results to prevent relapse in opioid dependence. In South and South-East Asia, naltrexone is available in some jurisdictions as a tablet taken daily, though it is available in a long-acting injectable form and as an implantable preparation in other parts of the world. There is insufficient evidence to recommend these latter preparations for relapse prevention in

opioid dependence, although in theory these long-acting preparations should improve adherence. Naltrexone may also be expensive.

Naltrexone is prescribed as 25 mg in tablet form on the first day followed by 50 mg taken daily thereafter for a number of months, sometimes years, depending on clinical progress. Adherence is crucial to effectiveness and can be boosted if directly observed. Health professionals or supportive family members can provide supervised administration. Naltrexone does not need to be tapered on cessation as it produces no marked withdrawal symptoms.

	Day 1	Day 2	Thereafter
Total daily dose (mg) (once daily)	25	50	50

Naltrexone may exacerbate depression and should be used with caution in depressed individuals unwilling or unable to treat their depression. Naltrexone should not be used in individuals with end-stage liver disease. The presence of opioids will lead to acute withdrawal after administration of naltrexone and individuals should be counselled to avoid all opioids for at least 24 hours prior to commencement of naltrexone therapy. Individuals using opioids while on naltrexone should be counselled on the increased risk of overdose. Naltrexone will result in a reduced tolerance for opioids as patients adapt to being free of regular opioids. In addition, a high dose of opioids is generally needed to override the effect of naltrexone, which can lead to overdose.

Naltrexone is further discussed in Appendix B.

## OTHER CONSIDERATIONS

# 9

### 9.1

#### Legal responsibilities

All therapeutic opioids are controlled substances and so adherence to legislative frameworks is critical. Key components to which particular attention should be paid are:

- Prescribing only where clinically indicated
- Not self-prescribing or self-administering
- Ensuring that prescriptions are written correctly and legibly
- Registering the patient with the indicated authority
- Supplying the controlled substance only with a valid prescription
- Ensuring secure storage of controlled substances
- Accurate and timely record-keeping.

Legal frameworks are complicated and vary substantially within and between countries of South and South-East Asia. All health professionals working in the area of treatment of opioid dependence should be aware of the local regulations within which they work and, in particular, of any new changes.

### 9.2

#### Confidentiality

Confidentiality is paramount to good clinical care. It can also increase the rate of retention in treatment. Clinical information should be provided to others only with the patient's written consent.

### 9.3

#### Driving while on OST

Patients should be counselled on the risk of driving while on opioids. Opioids

are sedating and may impair the ability to perform complex tasks, particularly when dose levels peak, e.g. two hours after methadone dosing. Particular care should be taken when OST is initiated or the dose of the opioid is changed. Patients engaging in polysubstance use with other sedatives may be further impaired.

## 9.4 Forms

Standardized forms can benefit a treatment service by:

- Enhancing standardization and consistency of service provision
- Simplifying evaluation.

The following forms are recommended during normal clinical practice:

- Contact details
- Clinical assessment form – completed by the clinician
- Notification of commencement of OST sent to the registration agency on commencement of treatment
- Notification of termination of OST sent to the registration agency on termination of treatment
- Dosing card or standardized prescription
- Consent for treatment.

The following information sheets for patients are recommended during provision of normal clinical services:

- Information about methadone
- Information about buprenorphine and buprenorphine/naloxone
- Information about naltrexone therapy
- Information about substance use and dependence including opioids, ATS, cannabis, benzodiazepines, inhalants, alcohol and any other psychoactive substances pertinent to the local context – including treatment options
- Information about harm reduction such as the prevention of bloodborne virus transmission including HIV and hepatitis B and C
- Information about STIs and their treatment
- Information on TB and its treatment

#### Other considerations

- Information on mental health conditions including depression, anxiety, bipolar disorder and psychosis and their treatment
- Information about pregnancy and contraception
- Information about prevention of overdose

## 9.5

### Referral for clinical and support services

The importance of strong referral systems cannot be overemphasized. Referral systems are dependent on relationships between services and their personnel. An inventory of local services for referral relevant to the needs of persons with substance use issues should be conducted by any drug treatment service so all staff are aware of the services available to their patients. Relevant services include most health and welfare agencies, including those providing emergency accommodation. Contact details should be readily available to clinical staff to facilitate referral.

## 9.6

### Record-keeping

Patient notes should be adequate and legible to another clinician who may be involved in the care of the patient. Patient records are confidential and should be stored as such. Patient records are generally stored for a number of years after the patient has been discharged from care.

Electronic patient record systems are emerging as an alternative to paper-based systems; however, these require substantially greater resources and are therefore only available in major centres, if at all.





# APPENDICES



# APPENDIX A

## SAMPLE ASSESSMENT RECORD FOR DRUG DEPENDENCE AND PSYCHOSOCIAL ASSESSMENT\*

### Patient identification and demographic information

#### Drug use history

	Age at first use	Quantity	Frequency	Route of administration	Duration	Use in past 90 days
Alcohol						
Tobacco						
Cannabis						
Opiates						
Amphetamines						
Ecstasy or other ATS						
Cocaine						
Hallucinogens						
Inhalants						
Sedatives						
Other (specify)						

ATS amphetamine-type stimulants

\*From *Treatment and care for HIV-positive injecting drug users: initial patient assessment – module 3* (Jakarta, ASEAN/USAID/WHO/FHI, 2007).<sup>37</sup>

Drug dependence

ICD-10 Assessment of dependence	Yes Dependence identified	No Dependence not identified
If Yes, record drug(s):		

Last withdrawal	Date
Complications	

Problems relating to drug use	Duration of the problem

Previous drug use treatment/intervention

When	Type of intervention	Where	Duration	Outcome

Mental health

Kessler Psychological Distress Scale		
Patient's score	Kessler 10 score	Level of anxiety or depressive disorder
	10–15	Low or no risk
	16–29	Medium risk
	30–50	High risk

Psychotic symptoms or signs

Past history of mental illness

Family history of mental illness

Suicidality

Current
Past
When
How
Why

Social assessment

Marital status
Family
Friends and social networks
Financial and employment circumstances
Accommodation
Education
Legal issues
Major life events/crises
History of trauma
Personality traits
Eating patterns

Patient's goals

--

Problem areas identified

--

Agreed plan

--

## APPENDIX B

### PHARMACOLOGY AND TOXICOLOGY OF METHADONE, BUPRENORPHINE AND NALTREXONE

Methadone and buprenorphine are potentially toxic drugs and so it is important to understand their pharmacology.

#### 11.1 Methadone

##### 11.1.1 Clinical pharmacology

Methadone is a synthetic opioid that acts as a full agonist at the  $\mu$  (mu) opiate receptor. It is well absorbed orally, but has a slow onset of action, with a peak effect 2–4 hours after administration, though levels in the cerebrospinal fluid peak over 3–8 hours after dosing. It has a half-life of around 24 hours. It is relatively lipid soluble resulting in good transfer across the blood–brain barrier and 90% is bound to plasma proteins distributed throughout the body’s fluid compartments. Over time (days), the levels of methadone in these different compartments and organs equilibrate. During chronic use, methadone accumulates in the liver. More than 50% of methadone is metabolized in the liver by cytochrome p450-related enzymes (primarily 3A4 and to a lesser extent 2D6 and 1A2), hence its interactions with some ARV medications. Individual genetic differences in the cytochrome p450 system may help explain variations in methadone metabolism between individuals. Methadone can induce this enzyme system so it is metabolized faster by those on long-term methadone.

##### 11.1.1.1 Pharmacokinetic interactions

Medications that inhibit or induce the cytochrome p450 system (3A4, 2D6 and 1A2) may affect metabolism, thereby increasing or decreasing levels when commenced or ceased.

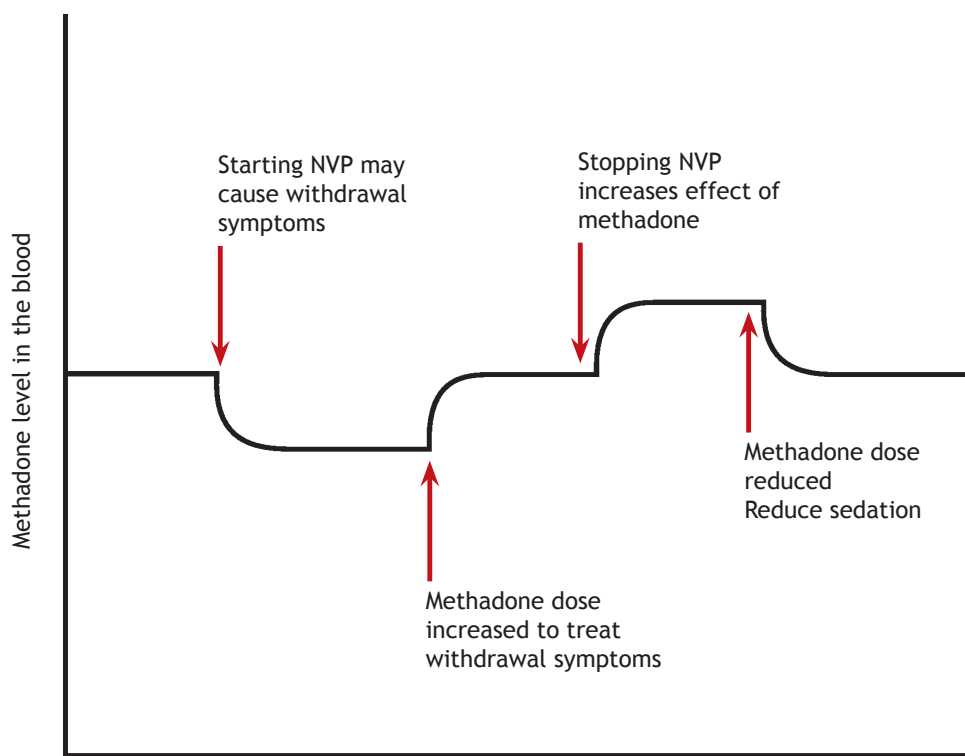
### 11.1.1.1.1

#### *Medications that increase methadone metabolism*

Patients starting on these medications may need an increase in their methadone dose:

- Some antiepileptics such as phenytoin, phenobarbitone and carbamazepine
- Some ARVs including nevirapine and efavirenz and, to a lesser extent, ritonavir, nelfinavir and lopinavir–ritonavir
- Some antibiotics including rifampicin used in TB treatment

**Figure 4.** Interaction between methadone and nevirapine (NVP)



### 11.1.1.1.2

#### *Medications that reduce methadone metabolism*

Patients commencing on these medications may need to decrease their methadone dose:

- Some selective serotonin reuptake inhibitors (SSRIs) including sertraline and fluvoxamine
- Some antifungals including fluconazole
- Some histamine antagonists including cimetidine

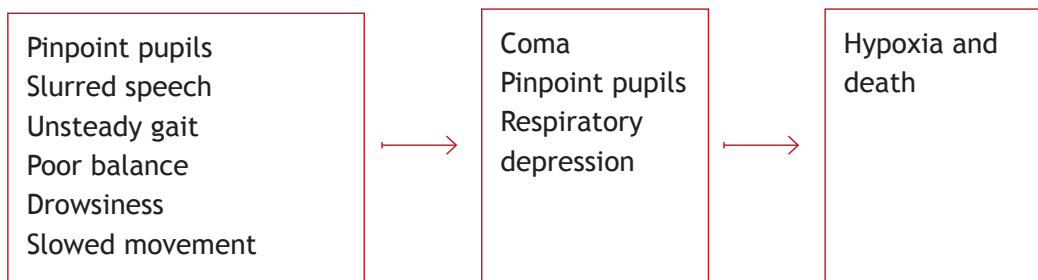
### 11.1.1.2 Pharmacodynamic interactions

Pharmacodynamic interactions refer to medication synergy through similar mechanisms of action. All CNS depressants (medications that sedate) have the potential to interact with methadone and increase the risk of overdose. These include:

- Other opioids
- Benzodiazepines
- Alcohol
- Tricyclic antidepressants such as amitriptyline.

### 11.1.2 Toxicology

Methadone is a potentially toxic substance. Death results from hypoxia due to respiratory depression, usually the result of interactions with other sedatives, of which benzodiazepines are the most common.



#### 11.1.2.1 Treatment of methadone overdose

Patients on long-term methadone can be watched for 4–6 hours. If there are no signs of toxicity, the patient can be discharged home to return the next day. Patients naive to the effects of methadone or experiencing clinical methadone overdose as described in the figure above should be referred to the nearest hospital.

Naloxone should be used with caution due to its short half-life, as methadone will continue to produce respiratory depression after the effects of naloxone have worn off.

Treatment of methadone overdose should be as follows:

- Respiratory support
- Continuous administration of naloxone either as boluses or infusion if appropriate.

## 11.2 Buprenorphine

Buprenorphine and a buprenorphine–naloxone combination are discussed here. The addition of naloxone to buprenorphine does not affect the pharmacology or toxicology of buprenorphine.

### 11.2.1 Clinical pharmacology

Buprenorphine is a partial agonist at the  $\mu$  opiate receptor and an antagonist at the kappa opiate receptor. It has a strong affinity for the receptor and thus a long half-life (up to 37 hours). It has a high first-pass metabolism in the liver and so is administered sublingually to increase blood levels. When buprenorphine is given in combination with naloxone and administered sublingually, the naloxone does not affect the absorption of buprenorphine. Only 3% of naloxone administered sublingually is absorbed, thereby having little effect. Peak effect occurs 1–2 hours after administration. It is heavily (96%) bound to protein in the blood and has a large volume of distribution. It is mostly metabolized in the liver by the cytochrome p450 system (CYP-3A4) and glucuronidation. Twenty-five per cent is excreted unchanged by the kidneys. Buprenorphine has active metabolites.

Due to its antagonist action on the kappa opioid receptor, at very high doses (supratherapeutic) buprenorphine acts as an opioid antagonist.

#### 11.2.1.1 Pharmacokinetic interactions

Although buprenorphine is a strong inhibitor of CYP-3A4 and 2D6, clinically there is little effect due to the low levels of buprenorphine required in therapeutic dosing.

### 11.2.1.2

#### Pharmacodynamic interactions

Buprenorphine can produce respiratory depression but usually only in the presence of other sedating agents, particularly benzodiazepines. Buprenorphine tends to displace other opioids, reversing their effects – known as a precipitated withdrawal.

### 11.2.2

#### Toxicology

The respiratory depression associated with an overdose of buprenorphine may well be due to the effects of another agent such as alcohol or benzodiazepines. Treatment of an overdose of buprenorphine is difficult as naloxone is ineffective in reversing it. For this reason, patients should be treated in hospital. Treatment is restricted to supportive ventilation and correction of other underlying causes.

## 11.3

### Naltrexone

#### 11.3.1

##### Clinical pharmacology

Naltrexone is an antagonist at the opiate receptor. It has a high receptor affinity and displaces other opioids. It is long-acting and has a half-life of up to four days. It is metabolized in the liver. Very little is excreted unchanged in the urine. It is administered as a 50 mg tablet daily.

##### 11.3.1.1

##### Pharmacokinetic and pharmacodynamic interactions

The interactions of naltrexone have not been studied in detail. However, it appears that naltrexone has few, if any, interactions with other medications, apart from opioids. Naltrexone blocks the effects of opioids and causes abrupt withdrawal if administered in the presence of opioids. If opioids are administered in the presence of naltrexone, the effect of the opioids will be markedly reduced – if there is any effect at all. Despite this, high-dose opioids may displace naltrexone at the opioid receptor and for this reason and lack of opioid tolerance, individuals on naltrexone remain at risk for overdose.

### 11.3.2

#### Toxicology

Naltrexone is relatively safe even at higher-than-normal doses. Overdose may cause mild liver inflammation and nausea. Treatment of overdose should be symptomatic with supportive therapy given as required.

# APPENDIX C

## FEATURES OF A METHADONE OR BUPRENORPHINE PRESCRIPTION

The following is an example of a prescription for methadone.#

Dr ABC Prescriber \_\_\_\_\_ your name, address,  
Drug Treatment Centre \_\_\_\_\_ contact details  
Helpful Hospital  
Phone 01 222 3333

29/10/2010 \_\_\_\_\_ date

Maung AB Patient \_\_\_\_\_ patient's name  
123A Home Street \_\_\_\_\_ and address  
Friendly Township

Rx Methadone Solution 5 mg/ml \_\_\_\_\_ script written indelibly in ink

Dispense 60 mg (sixty) \_\_\_\_\_ dose in words and figures

from: 30 October 2010 \_\_\_\_\_ date of first dose on this script

until: 29 November 2010 inclusive \_\_\_\_\_ date of last dose on this script

\_\_\_\_\_ for computer-generated script,  
particulars of script also  
handwritten



\_\_\_\_\_ signature

To be dispensed at: \_\_\_\_\_ pharmacy at which methadone  
DTC Dispensary \_\_\_\_\_ is to be dispensed  
Helpful Hospital

#Taken from *Guidelines on methadone in Myanmar for prescribers and dispensers*. Yangon, Department of Health, Ministry of Health, Union of Myanmar/WHO, 2004.<sup>38</sup>

## APPENDIX D

### SAFE PRESCRIBING RECOMMENDATIONS FOR THOSE NOT APPROVED TO PRESCRIBE METHADONE

Given the risks of toxicity associated with methadone treatment, if the prescriber is unfamiliar with the risks of methadone treatment then they must be extremely cautious when prescribing for patients. For stable patients requiring only the continuation of an expired prescription without an increase of dose or take-away frequency:

- Take a thorough history and examine the patient.
- Check with the dispensary that the patient has attended regularly for daily dosing.
- Contact the specialist at the drug treatment centre:
  - if there are any management problems or concerns about the safety of the patient
  - if a dose increase or take-away dose appears necessary. Do not provide an increased dose or take-away dose unless advised to do so by the specialist. Document the advice given and the name of the consultant in the patient's notes.

All deputizing practitioners should manage the patient as follows:

- Continue the usual prescriber's management plan and dosage regimen as documented in the clinical record. (It is acceptable to reduce the dose if the patient is experiencing toxicity.)
- Note on the prescription that you are temporarily deputizing for the patient's usual prescriber.
- Limit the duration of the prescription to the expected period of absence of the usual prescriber, indicating precise starting and completion dates.
- Arrange for the usual prescriber to review the patient as soon as possible thereafter.

- Document details of consultations and methadone prescriptions in the patient's notes.

In addition, ensure that the prescription gives clear, unequivocal directions to the dispenser, including:

- The precise dose in words and figures
- The precise starting date
- The date of the last dose to be given on this prescription
- The name of the dispensing site at which it is to be dispensed.

Treatment should not be initiated or transfer of patients arranged between dispensing sites without discussion with a consultant at a major drug treatment centre.

**Before authorizing take-away doses:**

- Contact the dispensing site to confirm the regularity of dosing and the patient's progress.
- Ensure the patient is stable and meets all the criteria specified in these guidelines.

## APPENDIX E

### INTERACTIONS BETWEEN OPIOID SUBSTITUTION THERAPY AND COMMONLY USED MEDICATIONS

Interactions between methadone or buprenorphine and commonly used medications for HIV and TB generally occur as a result of an alteration in the metabolism of the OST by the hepatic cytochrome p450 system. ART–OST interactions may result in symptoms of withdrawal or oversedation requiring dose adjustment.

The effect of methadone or buprenorphine on some ARVs may result in reduced viral suppression or an increase in side-effects. Patients on ART should be monitored when commenced on methadone or buprenorphine, or when the ART regimen is changed.

Further information about the management of HIV in injecting drug users can be found in various guidance documents.<sup>30,31,39,40</sup>

#### 14.1

#### Interactions between ARVs and methadone\*

ARV	Effect of ARV on methadone	Effect of methadone on ARV	Comments
<b>Nucleoside reverse transcriptase inhibitors (NRTIs)</b>			
Zidovudine (AZT)	None reported. No dosage adjustments necessary	Concentrations increased (43%). Clinical significance unclear. Adverse events possible	Monitor for adverse events of AZT. Monitor for anaemia, neutropenia, nausea, myalgia, vomiting and headache
Lamivudine (3TC)	None reported	None reported	No known interactions

\*From *Management of HIV infection and antiretroviral therapy in adults and adolescents: a clinical manual* (New Delhi, World Health Organization Regional Office for South-East Asia, 2007),<sup>30</sup> and *Treatment and care for HIV-positive injecting drug users: drug interactions – module 8* (Jakarta, ASEAN/USAID/WHO/FHI, 2007).<sup>31</sup>

ARV	Effect of ARV on methadone	Effect of methadone on ARV	Comments
<b>Nucleoside reverse transcriptase inhibitors (NRTIs) contd</b>			
Emtricitabine (FTC)	Not studied	Not studied	No known interactions
Stavudine (d4T)	None reported	May reduce d4T levels by 27%	No dose adjustment usually required
Tenofovir disoproxil fumarate (TDF)	None reported. No dosage adjustments necessary	None reported. Concentrations decreased (18–27%)	No known interactions. No dose adjustment of d4T required
Abacavir (ABC)	Slight decrease in methadone level. Risk of opioid withdrawal low. Dosage adjustments unlikely but some patients might require increase in methadone dose	Concentrations decreased by 34%	Risk of opioid withdrawal low. Methadone dose adjustment might be needed. No dose adjustment of ABC required
Didanosine (ddI) buffered tablet enteric-coated (EC) capsule	None reported. No dosage adjustments necessary	Concentrations decreased by 60% when buffered tablet taken, but not with EC capsule	Avoid use of ddI buffered tablets. Use EC capsule if available
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</b>			
Efavirenz (EFV)	Decrease in methadone level by up to 60%. Symptoms of opioid withdrawal common	Unknown	Observe for symptoms of methadone withdrawal and increase dosage as necessary. Considerable increase in methadone dose (50%) usually required
Nevirapine (NVP)	Decrease in methadone level by 46%. Symptoms of opioid withdrawal common	None reported	
<b>Protease inhibitors (PIs)</b>			
Lopinavir/ritonavir (LPV/r)	Decrease in methadone level by 26–53%	None reported	May require increase in methadone dose
Saquinavir (SQV)	None reported	None reported	Studies limited, but monitor for need to increase methadone dose

## 14.2

## Interactions between ARVs and buprenorphine\*

ARV	Effect of ARV on buprenorphine	Effect of buprenorphine on ARV	Comments
<b>Nucleoside reverse transcriptase inhibitors (NRTIs)</b>			
No significant interactions reported			
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</b>			
Efavirenz (EFV) and nevirapine (NVP)	Buprenorphine concentrations decreased but not significant	None reported	No dose adjustment of EFV and NVP required
<b>Protease inhibitors (PIs)</b>			
Ritonavir (RTV) Atazanavir (ATV)	Inhibition of buprenorphine metabolism resulting in a clinically significant increase in buprenorphine levels	None reported	Buprenorphine dose may need to be reduced

## 14.3

## Interactions of methadone with other medications†

Drug (indication)	Effect on methadone	Comments
Rifampicin (TB)	Decrease in methadone level by 33–68% and may induce symptoms of opioid withdrawal	Increase in methadone dose required if withdrawal symptoms present
Sertraline (antidepressant)	Increase in methadone levels by 26%	Associated with cardiac rhythm disturbances, caution when used with methadone. No dose adjustments required

\*From *Management of HIV infection and antiretroviral therapy in adults and adolescents: a clinical manual* (New Delhi, World Health Organization Regional Office for South-East Asia, 2007) and <http://www.hivguidelines.org/GuideLine.aspx?guideLineID=50> (accessed on 26 September 2008)<sup>30,40</sup>

†From *Management of HIV infection and antiretroviral therapy in adults and adolescents: a clinical manual* (New Delhi, World Health Organization Regional Office for South-East Asia, 2007) and *Treatment and care for HIV-positive injecting drug users: drug interactions – module 8* (Jakarta, ASEAN/USAID/WHO/FHI, 2007).<sup>30,31</sup>

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Drug (indication)	Effect on methadone	Comments
Carbamazepine and phenytoin (anticonvulsants)	Decrease in methadone levels and may cause symptoms of methadone withdrawal	Increase in methadone dose may be required. Consider using sodium valproate as an alternative
Fluconazole (antifungal)	Increase in methadone levels by 35%	Clinical significance unknown

## APPENDIX F

### OPIOID SUBSTITUTION THERAPY GUIDELINES FOR DISPENSERS

A comprehensive set of guidelines for dispensers is beyond the scope of this document but key issues are discussed below.

#### 15.1

##### Key factors in dispensing OST

- Correctly identify the patient prior to dosing.
- Ensure the dose is authorized by the prescriber.
- Confirm it is safe to administer the dose.
- Supervise dosing.
- Communicate with the prescriber regarding irregularities in the patient's attendance.
- Keep adequate records.

Right person    Right drug    Right dose    Right route    Right time    Write down!

#### 15.2

##### Components of a dispensing system

##### 15.2.1

###### Approval

The regulation of OST will vary by jurisdiction. Dispensing agencies and staff should be:

- Aware of the local regulatory framework and clinical dispensing guidelines
- Trained in dispensing OST
- Authorized as trained dispensers

## 15.2.2

### Development of procedures

Dispensing agencies should develop procedures to ensure adherence to local regulatory frameworks when handling methadone or buprenorphine. Staff should be trained in these procedures.

## 15.2.3

### Storage

Methadone, buprenorphine, other opioids and benzodiazepines are generally regulated substances and should be stored in secured areas in accordance with local controlled drug laws. These substances do not need refrigeration.

## 15.2.4

### Patient records

Records of dispensing should be kept. The components include the following:

- Name and date of birth of the patient (or another identifier to differentiate in the case of identical names)
- A photo if possible
- Type of treatment and dosage – may also be written in words to reduce misreading
- Route of administration
- Dates between which the prescription is valid
- All prescriptions should be written in milligrams (mg) to avoid confusion in dosing where methadone is mixed at variable concentrations.
- A record of each dose dispensed, signed by the dispenser
- Space for ancillary notes about adverse events or situations

## 15.3

### Guidelines for dispensing

## 15.3.1

### Accepting new patients

Some jurisdictions will restrict the number of patients a single dispenser can dispense to concurrently. Dispensers should be aware of all new patients.

Where possible, dispensers should attempt to develop strong and respectful relationships with patients from the start of treatment in order to improve care and strengthen patient engagement.

An intake procedure should be adopted, which might include the following components:

- Identification including photograph signed by the prescriber
- A valid prescription
- A phone call or fax to/from the prescriber to confirm the background and other significant information
- A brief interview including an outline of pharmacy hours and rights and responsibilities of the patient while engaged in the programme.
- Some dispensers may enter into a written agreement with the patient regarding adherence to dispensing policies.

### 15.3.2

#### Prescriptions

Patients should not be dosed without a valid prescription. In emergencies, a verbal order from the prescriber may be necessary, with a valid prescription forwarded as soon as practicable.

### 15.3.3

#### Preparation of doses

Methadone should be mixed to a standard concentration – usually 5 or 10 mg/ml. A dispensing site should use the same concentration for all patients to minimize incorrect dosing. Methadone can be mixed with juice or cordial to improve the taste. A syringe or displacement pump is recommended to ensure accurate dosing. Doses should be prepared at the time of dosing.

Take-home methadone should be accurately labelled. Some dispensing sites may mix methadone with cordial to increase the total volume in order to reduce illicit injection of take-home methadone. This may reduce the shelf-life of methadone, particularly in warm climates.

Buprenorphine may be crushed prior to administration to reduce the risk of diversion and injection.

### 15.3.4

#### Administration of doses

**Supervised doses should *always* be directly observed. Dispensing areas should be discrete to avoid stigma.**

Methadone should be consumed in full view of the dispenser. There should be no remaining methadone visible in the mouth of the patient.

Buprenorphine-based therapy should, where possible, be crushed before administration. Patients should place the buprenorphine under the tongue and be asked to close their mouth and wait in view of the dispenser for 2–7 minutes. Patients should be encouraged not to swallow and asked “How is the tablet dissolving?” Inspection under the tongue should reveal complete dissolution of buprenorphine. Although this ritual might appear invasive, patients usually adapt quickly. Post-dissolution inspection may not have to be done every time, though patients should wait 2–7 minutes after each dose.

### 15.3.5

#### Transferred patients

When patients are transferred from another dispensing site, dispensers should confirm the time of dosing, medication type and quantity of last dose. Confirmation should be written or verbal with follow-up written (faxed) information. This approach minimizes the risk of dosing the same patient on the same day at two different sites, and thus reduces the risk of overdose.

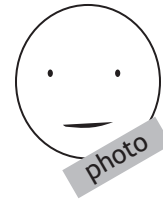
### 15.3.6

#### Termination of treatment

Termination of treatment by a dispenser should occur only in consultation with the prescriber. An alternate dispenser should be found. In the case of escalating difficulties with a patient, an alternative dispensing location should be found early – a change in environment may defuse the situation.

### 15.3.7 Example of an OST dispensing card

Methadone dispensing card



Drug treatment centre/dispensary.....  
 Name..... DOB.....  
 Registration number.....  
 Methadone/buprenorphine (circle appropriate)

Date	Time	Dose (mg)	Dose (ml)	Patient signature	Dispenser signature	Comment

## APPENDIX G

### NEONATAL ABSTINENCE SYNDROME

Neonatal abstinence (withdrawal) syndrome (NAS) occurs in 60% of neonates exposed to opioids *in utero*. Heroin withdrawal usually occurs within the first 48 hours of life. Methadone withdrawal can occur up to two weeks after birth, but usually occurs within the first 96 hours after birth. The syndrome is typically an autonomic multisystemic reaction, the symptoms of which are mostly neurological and may be prolonged.

All babies born to opioid-dependent mothers should undergo normal postnatal monitoring. In addition, use of specific assessment tools (e.g. modified Finnegan neonatal abstinence syndrome score [NASS]) should commence two hours after birth and subsequently every four hours.<sup>34</sup> The assessment tool is usually scored every four hours (half to one hour after feeds) with pharmacological treatment initiated when three consecutive scores average more than or are equal to 8; or when two consecutive scores are more than or equal to 12.

**Table 15.** Neonatal abstinence (withdrawal) syndrome scoring chart for term infants (Modified Finnegan NASS)<sup>33,34</sup>

System	Signs	Score	Date and time
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	
	Generalized convulsions	5	

System	Signs	Score	Date and time
Metabolic/ vasomotor/ respiratory disturbances	Fever (37.3–38.3°C)	1	
	Fever (38.4°C and higher)	2	
	Frequent yawning (3–4 times in a row)	1	
	Nasal stuffiness	1	
	Sneezing (>3–4 times in a row)	1	
	Nasal flaring	2	
	Respiratory rate >60/min	1	
	Respiratory rate >60/min with retractions	2	
Gastrointestinal disturbances	Excessive sucking	1	
	Poor feeding	2	
	Regurgitation	2	
	Projectile vomiting	3	
	Loose stools	2	
	Watery stools	3	
TOTAL SCORE			
Scorer's initials			

## 16.1 Treatment

### Supportive care

Use a pacifier, swaddle and closely wrap the infant, give small frequent feeds and ensure close skin contact with mother.

### Specific treatment

Opioids are preferred. A Finnegan score of 8 or more on three consecutive occasions or 12 or more on two consecutive occasions indicates the need to commence pharmacotherapy:

**Morphine elixir 1 mg/ml:** If available may be used as an alternative to diluted tincture of opium.

**Starting dose:** 0.02 mg/kg orally 4–6 hourly

**Maintenance dose:** 0.02 mg/kg orally 4–6 hourly; increase by 0.02 mg/kg at the end of every 4-hour period until the desired response is achieved; maintain dose for 3–5 days; then begin tapering the dose by 10% (of peak dose) every 2–3 days.

**Sedatives** can also be used to treat NAS. Phenobarbitone, diazepam and chlorpromazine have all been used in this context but the control of symptoms, convulsions and return to normal feeding are not as satisfactory as with opioids. The presence of non-opioid withdrawal symptoms (e.g. benzodiazepines, less commonly alcohol or rarely, cannabis or amphetamines) resulting in a Finnegan score of 8 or more on three consecutive occasions, or 12 or more on two consecutive occasions indicates the need to commence pharmacotherapy.

**Phenobarbitone** 5 mg/kg/day in two divided doses is titrated to achieve symptom control.

Until weaning of the dose has begun, constantly monitor the neonate's vital signs and oxygen saturation.

Adverse effects of morphine and phenobarbitone include sedation and constipation (less likely with phenobarbitone); overdosing with morphine may cause narcosis, manifested by decreased reflexes and poor Moro reflex, and diminished sucking, grasping and response to pain. More profound narcosis includes hypotonia, obtundation, coma, irregular shallow respiration, apnoea, bradycardia and hypothermia.

If signs of opioid toxicity are observed, **do not** give naloxone as withdrawal seizures can occur. Provide respiratory support.

NAS and its treatment may require a 2–4-week postnatal admission period. Particular attention is required over this time to establish satisfactory breastfeeding and normal maternal bonding processes.

### 17.1 Comparative table of opioids

The following table gives approximate conversions between different opioid agonists.

Table 16. Opioid equivalence table

Drug	Dose equivalent to 10 mg oral morphine <sup>1</sup>	Approximate duration of action (hours) <sup>2</sup>
<b>Agonists</b>		
Codeine <sup>3</sup> (analgesic only)	65 mg oral	3–4
Dextropropoxyphene <sup>3</sup>	unknown	4–6
Fentanyl	30–50 µg IV/SC	0.5–1
Hydromorphone <sup>3</sup>	0.5–0.7 mg SC/IM; 2–2.5 mg oral	2–4
Methadone (analgesic only)	10 mg SC/IM; 20 mg oral <sup>4</sup>	8–24 (chronic dosing)
Methadone (chronic use in maintenance)	1 mg oral	8–24 (chronic dosing)
Morphine <sup>3</sup>	10 mg oral 3–4 mg SC or IM	2–3; 12–24 (controlled release)
Oxycodone	5–7 mg oral	3–4; 12–24 (controlled release)
Pethidine <sup>3</sup>	25–35 mg IM	2–3
Tramadol <sup>3</sup>	30–40 mg IM/IV; 50 mg oral	3–6
<b>Partial agonists</b>		
Buprenorphine (analgesic only)	0.3 mg sublingual	6–8 <sup>5</sup>

- <sup>1</sup>Doses given are a guide only  
<sup>2</sup>Duration of action depends on dose and route of administration  
<sup>3</sup>Active metabolites which may prolong action  
<sup>4</sup>Based on single-dose studies  
<sup>5</sup>Duration of action is extended in higher doses used in OST

Adapted from *Australian medicines handbook, 2007*<sup>41</sup>

## 17.2 Benzodiazepine comparative table

The following table gives approximate conversions between different benzodiazepines.

**Table 17.** Benzodiazepine equivalence table

Drug	Equivalence of oral dose (mg) <sup>1</sup>	Duration of action
Triazolam	0.25	Short
Clonazepam	0.25	Long
Alprazolam	0.5	Intermediate
Lorazepam	2	Intermediate
Flunitrazepam	1	Intermediate
Diazepam	5	Long
Oxazepam	15	Intermediate
Temazepam	10	Intermediate
Flurazepam	15	Long
Zolpidem <sup>2</sup>	0	Short
Zopiclone <sup>2</sup>	7.5	Intermediate

<sup>1</sup> Approximate

<sup>2</sup> Zolpidem and zopiclone are non-benzodiazepines which act in a similar fashion to benzodiazepines. Adapted from *Goodman and Gilman's Pharmacological basis of therapeutics, 2007*; *Micromedex® healthcare series, 2007*<sup>42,43</sup>

- <sup>1</sup> WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. Geneva, World Health Organization, 2008.
- <sup>2</sup> Mathers BM et al.; for the 2007 Reference Group to the UN on HIV and Injecting Drug Use. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. *Lancet*, 2008, DOI:10.1016/50140-6736(08)61311-2.
- <sup>3</sup> International Harm Reduction Association. What is harm reduction? <http://www.ihra.net/Whatisharmreduction> (accessed on 24 August 2008).
- <sup>4</sup> [http://www.searo.who.int/LinkFiles/Publications\\_BiregionalStrategicPlan.pdf](http://www.searo.who.int/LinkFiles/Publications_BiregionalStrategicPlan.pdf) (accessed on 24 August 2008).
- <sup>5</sup> Wodak A. Controlling HIV among injecting drug users: current status of harm reduction. Presentation made at the International AIDS Conference, Toronto, 15 August 2006. Available at: <http://www.aids2006.org/Web/TUPL04.ppt#1> (accessed on 24 August 2008).
- <sup>6</sup> UNGASS. Declaration of Commitment on HIV/AIDS, New York, 2001. <http://www.unaids.org/en/AboutUNAIDS/Goals/UNGASS/> (accessed on 2 September 2008).
- <sup>7</sup> G8 Gleneagles Summit, Perthshire, 2005. [http://www.wpro.who.int/sites/hsi/universal\\_access/](http://www.wpro.who.int/sites/hsi/universal_access/) (accessed on 28 August 2008).
- <sup>8</sup> WHO/UNAIDS/UNODC. *Substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention: position paper*. Geneva, WHO, UNAIDS and UNODC, 2004.

- <sup>9</sup> WHO. *Evidence for action: Policy briefs and technical papers on HIV/AIDS and injecting drug users*. Geneva, WHO, 2004, 2005, 2006. <http://www.who.int/hiv/pub/idu/idupolicybriefs/en/index.html> (accessed on 24 August 2008).
- <sup>10</sup> WHO/UNAIDS/UNODC. *Evidence for action on HIV/AIDS and injecting drug use. Policy brief: reduction of HIV transmission through drug-dependence treatment*. Geneva, WHO, 2004. Available at: <http://www.who.int/hiv/pub/advocacy/en/drugdependencetreatmenten.pdf> (accessed on 24 August 2008).
- <sup>11</sup> WHO/UNAIDS/UNODC. *Evidence for action technical papers. Effectiveness of drug dependence treatment in preventing HIV among injecting drug users*. Geneva, WHO, 2005. Available at: <http://www.emro.who.int/aiecf/web203.pdf> (accessed on 28 August 2008).
- <sup>12</sup> WHO/UNAIDS/UNODC. *Evidence for action: effectiveness of community-based outreach in preventing HIV/AIDS among injecting drug users*. Geneva, WHO, 2004.
- <sup>13</sup> Hall W, Ward J, Mattick RP. Introduction. In: Ward J, Mattick RP, Hall W (eds). *Methadone maintenance treatment and other opioid replacement therapies*. Amsterdam, Harwood, 1998.
- <sup>14</sup> Stimson GV, Fitch C, Rhodes T. *The rapid assessment and response guide on injecting drug use (IDU-RAR)*. Draft for field-testing. Geneva, WHO, 1998. Available at: [http://www.who.int/substance\\_abuse/publications/en/rar\\_review.pdf](http://www.who.int/substance_abuse/publications/en/rar_review.pdf) 2003 (accessed on 26 August 2008).
- <sup>15</sup> Marsden J, Ogborne A, Farrell M, Rush B. *International guidelines for the evaluation of treatment services and systems for psychoactive substance use disorders*. WHO, UNDCP, EMCDDA. Available at: [http://whqlibdoc.who.int/hq/2000/WHO\\_MSD\\_MSB\\_00.5.pdf](http://whqlibdoc.who.int/hq/2000/WHO_MSD_MSB_00.5.pdf) (accessed on 26 August 2008).
- <sup>16</sup> WHO/UNODC. *Principles of drug dependence treatment*. Vienna, WHO/UNODC, 2008. Available at: [http://www.who.int/substance\\_abuse/publications/principles\\_drug\\_dependence\\_treatment.pdf](http://www.who.int/substance_abuse/publications/principles_drug_dependence_treatment.pdf) (accessed on 26 August 2008)

- 17 WHO. *Brief intervention for substance use: a manual for use in primary care*. Geneva, WHO, 2005. Available at: [http://www.who.int/substance\\_abuse/activities/en/Draft\\_Brief\\_Intervention\\_for\\_Substance\\_Use.pdf](http://www.who.int/substance_abuse/activities/en/Draft_Brief_Intervention_for_Substance_Use.pdf) (accessed on 28 August 2008).
- 18 WHO. *ICD-10 symptom checklist for mental disorders: psychoactive substance use syndromes module*. Geneva, WHO, 2004.
- 19 National AIDS Control Organization (NACO). *Substitution therapy with buprenorphine for injecting drug users: practice guidelines*. New Delhi, Targeted Intervention Division, National AIDS Control Organization, Ministry of Health and Family Welfare, Government of India, 2008.
- 20 WHO. *Evidence for action: effectiveness of interventions to address HIV in prisons. Drug treatments*. Geneva, WHO, 2007.
- 21 WHO. *Regional guidelines for drug detoxification in closed settings*. Manila, WHO Regional Office for the Western Pacific, 2008.
- 22 Bien TH, Miller WR, Tonigan JS. Brief interventions for alcohol problems: a review. *Addiction*, 1993, 88:315–335.
- 23 Shand F, Gates J, Fawcett J, Mattick R. *Guidelines for the treatment of alcohol problems*. Sydney, National Drug and Alcohol Research Centre for the Commonwealth, Department of Health and Aging, 2003.
- 24 Ashton H. Protracted withdrawal from benzodiazepines: the post-withdrawal syndrome. *Psychiatric Annals*, 1995, 25:174–179.
- 25 ASEAN/USAID/WHO/FHI. *Treatment and care for HIV-positive injecting drug users: managing non-opioid drug dependence – module 5*. Jakarta, ASEAN/USAID/WHO/FHI, 2007:2–5.
- 26 Saunders JB et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction*, 1993, 88:791–804.

- <sup>27</sup> Babor TF et al. *AUDIT – the alcohol use disorders identification test: guidelines for use in primary care*. 2nd edition. Geneva, World Health Organization, 2001. Available at : [http://whqlibdoc.who.int/hq/2001/WHO\\_MSD\\_MSB\\_01.6a.pdf](http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6a.pdf) (accessed on 31 August 2008).
- <sup>28</sup> WHO/UNAIDS/UNODC. *Evidence for action technical papers. Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users*. Geneva, World Health Organization, 2005.
- <sup>29</sup> WHO. *Antiretroviral therapy for injecting drug users*. Geneva, World Health Organization, 2007.
- <sup>30</sup> WHO. *Management of HIV infection and antiretroviral therapy in adults and adolescents: a clinical manual*. New Delhi, World Health Organization Regional Office for South-East Asia, 2007.
- <sup>31</sup> ASEAN/USAID/WHO/FHI. *Treatment and care for HIV-positive injecting drug users: drug interactions – module 8*. Jakarta, ASEAN/USAID/WHO/FHI, 2007.
- <sup>32</sup> WHO. *Policy guidelines for collaborative TB and HIV services for injecting and other drug users: an integrated approach*. Geneva, World Health Organization, 2008.
- <sup>33</sup> New South Wales Department of Health. *National clinical guidelines for the management of drug use during pregnancy, birth and the early development years of the newborn*. Sydney, NSW Department of Health, 2008.
- <sup>34</sup> Finnegan L, Connaughton J, Kron R, Emich J. Neonatal abstinence syndrome: assessment and management. *Addictive Diseases*, 1975, 2(1–2):141–158.
- <sup>35</sup> Henry-Edwards S et al. *Clinical guidelines for the use of methadone in maintenance treatment of opioid dependence*. Canberra, Australian Government Department of Health and Aging, 2003.
- <sup>36</sup> Jittiwutikarn J et al. Comparison of tincture of opium and methadone to

control opioid withdrawal in a Thai treatment centre. *British Journal of Clinical Pharmacology*, 2004, 58:536–541.

- <sup>37</sup> ASEAN/USAID/WHO/FHI. *Treatment and care for HIV-positive injecting drug users: initial patient assessment – module 3*. Jakarta, ASEAN/USAID/WHO/FHI, 2007.
- <sup>38</sup> Ministry of Health/WHO. *Guidelines on methadone in Myanmar for prescribers and dispensers*. Yangon, Department of Health, Ministry of Health, Union of Myanmar/WHO, 2004.
- <sup>39</sup> WHO. *HIV/AIDS treatment and care. Clinical protocols for the WHO European Region*. Copenhagen, WHO Regional Office for Europe, 2007. Available at: <http://www.euro.who.int/Document/E90840.pdf> (accessed on 24 September 2008).
- <sup>40</sup> <http://www.hivguidelines.org/GuideLine.aspx?guideLineID=50> (accessed on 26 September 2008).
- <sup>41</sup> Rossi S (ed). *Australian medicines handbook 2007*. Adelaide, Australian Medicines Handbook, 2007.
- <sup>42</sup> Brunton LL, Lazo JS, Parker KL (eds). *Goodman and Gilman's Pharmacological basis of therapeutics*. 11th edition. New York, McGraw-Hill, 2007.
- <sup>43</sup> *Micromedex® healthcare series* [Intranet database]. Version 5.1. Greenwood Village, Colorado, Thompson Healthcare, 2007.



The South-East Asia Region is home to between 3.4 and 5.6 million injecting drug users. A large proportion of them resort to unsafe injecting practices such as sharing of needles and syringes. This has led to the rapid and large-scale transmission of HIV and hepatitis C in this population and their partners.

In order to prevent new infections, countries need to urgently expand the implementation of evidence-based drug treatment interventions. Opioid substitution therapy (OST) is the most useful and cost-effective intervention for managing opioid dependence and reducing the harms associated with it.

OST is now available in India, Thailand, Indonesia, the Maldives and Nepal, and will soon be introduced in Bangladesh. These practical guidelines aim to assist physicians and drug treatment professionals in establishing and delivering evidence-based, good quality, effective OST services in South-East Asia.



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