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GUIDELINES

MEDICATION-ASSISTED TREATMENT
FOR OPIOID DEPENDENCE IN NIGERIA:
METHADONE AND BUPRENORPHINE



European Union



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Medication-assisted treatment
for opioid dependence in Nigeria:
Methadone and Buprenorphine

2022



UNODC
United Nations Office on Drugs and Crime

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Foreword

The 2018 National Drug Use Survey (NDUS) revealed that nearly 14.4 per cent of Nigerians between the ages of 15-64 had used an illicit drug in the previous year, out of which approximately 4.6 million had used illicit prescription opioids and 87,000 had used heroin. The survey also showed that among the approximately 376,000 high-risk drug users (those who had used opioids, crack/cocaine or amphetamines in past 12 months, and at least five times in previous 30 days), nearly 90 per cent were opioid users.

Approximately 80,000 were people who inject drugs (PWID), with the majority injecting opioids (75 per cent). This survey also found that 9 per cent of PWID reported that they were living with HIV; it is highly likely these self-reported figures underrepresent actual prevalence. The national survey reported that only 12 per cent of people with high-risk drug use had ever received drug treatment, and just 4 per cent had received drug treatment in the previous year. In 2018, the estimated national prevalence of HIV among the general population was 1.4 per cent of Nigerians between ages 15-49, but was higher among PWID at 3.4 per cent, with the HIV prevalence among female PWID about five times greater than among male PWID (13.9 per cent vs 2.6 per cent).

These guidelines present, for the first time, a holistic and evidence-based national document for the provision of medication-assisted treatment for opioid dependence, in line with international best practices. To adapt these best practices to the Nigerian context, the guidelines were developed largely by Nigerian experts and practitioners in the field, allowing for the provision of evidence-based and effective services for people with opioid dependence in the country. The guidelines also serve as a reference for monitoring and evaluation of the quality of drug treatment services available to drug users.

The Government of Nigeria is committed to the implementation of these guidelines and the Federal Ministry of Health urges stakeholders to ensure that they are adopted and implemented such that evidence-based care may be provided to individuals in need, for the overall benefit of the Nigerian populace.



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Nigeria 2022

Preface

It is overwhelmingly evident that opioid addiction does not arise from an individual's lack of willpower and is therefore marginally amenable to a few psychosocial interventions. This makes medication-assisted treatment (MAT), a lifesaving intervention for persons who otherwise would continue in a downward spiral of opioid addiction, highly sought after by practitioners, clients and their families.

Over the past 100 years, MAT has evolved from a rudimentary and poorly understood application of pharmacology to a cutting-edge harm-reduction intervention of modern medicine. Countries implement varied systems for MAT mostly because methadone is an internationally controlled substance and diligence is required to prevent diversion by instituting effective and accountable supply chain systems that closely mirror the governance architecture in each country.

In Nigeria, methadone is procured centrally by the Federal Ministry of Health (FMOH) with support from the National Agency for Food and Drug Administration and Control, the competent national authority empowered to authorize importation of controlled substances. The supply chain for methadone in Nigeria is managed solely by the FMOH through the Department of Food and Drug Services (FDS). Working together with the FDS, the Drug Demand and Harm Reduction (DD/HR) Unit of the FMOH ensures the availability and accessibility of methadone and by extension MAT to persons eligible for the intervention across Nigeria.

This document avails the practitioner the much-needed guidance in managing clients with opioid addiction using MAT. Although pre-service curricula in medical training prescribe the teaching of MAT, it is worth mentioning that the contents are mostly skewed towards the provision of this intervention from a specialist standpoint. These guidelines, however, impart the requisite knowledge in the context of public health practice, which is in line with the guiding principles of universal health coverage. Therefore, internalizing the content of this guideline is pertinent to all members of the health workforce who are likely to be involved in the provision of this service.

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Nigeria 2022

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Accordingly, I appreciate the various experts from a wide range of sectors for their enormous contributions to the development of this document.

Let me specially thank the heads and relevant staff of the departments of Public Health, Food and Drug Services and the Drug Demand and Harm Reduction Unit of the Department of Hospital Services for their effective coordination and tireless efforts to develop these guidelines.

Finally, our gratitude goes to the Honourable Ministers for their support of the development of this document and the continuous commitment towards the prevention and control of drugs and substance abuse in Nigeria.



Mahmuda Mamman
Permanent Secretary
Federal Ministry of Health

Acronyms and abbreviations

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
ATS	Amphetamine-type stimulants
CBT	Cognitive-behavioural therapy
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CYP3A4	Cytochrome P450 enzyme CYP3A4
CYP2D6	Cytochrome P450 enzyme CYP2D6
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTS	HIV testing services
ICD	International Classification of Diseases
MAT	Medication-assisted treatment
NAS	Neonatal abstinence syndrome
NENDU	Nigerian Epidemiology Network of Drug Use
NSPs	Needle and syringe programmes
OAMT	Opioid agonist maintenance treatment
OST	Opioid substitution therapy
PWID	People who inject drugs
PWUD	People who use drugs
STI	sexually transmitted infection
SSRIs	Selective serotonin reuptake inhibitors
TB	Tuberculosis
TCAs	Tricyclic antidepressants
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization

Chapter 1

Background information



1. Introduction

In 2018, a large-scale drug use survey in Nigeria revealed the use of wide-ranging psychoactive substances, including an estimated 4.6 million people having used opioids (such as tramadol, codeine or morphine) for non-medical purposes in the previous 12 months. Of additional concern, an estimated 376,000 were considered high-risk people who use drugs (PWUD), with the majority believed to be regular users of opioids. It was also reported that in Nigeria an estimated 80,000 people injected drugs, commonly opioids.¹ In 2019, Nigeria conducted pilot Needle and Syringe Programmes (NSP) to service the needs of people who inject drugs (PWID). Access and utilization of NSP by PWID are widely considered fundamental components of any comprehensive and effective HIV-prevention programme. To complement NSP, and assist practitioners to provide the best care for persons with opioid use disorder, the introduction of medication-assisted treatment (MAT), accompanied with appropriate guidelines, has become critically important.

These guidelines were developed for specific health-care services and health-care professionals (practitioners, prescribers, dispensers, counsellors and other allied health workers) involved in the management of opioid dependence in Nigeria. These guidelines complement and provide an additional resource to the *National Guidelines for the Treatment of Substance Use Disorders for Nigeria* (2019),² with the goal of supporting Nigeria's efforts to increase the coverage and quality of effective treatment, including ethical responses for those experiencing substance use disorder. These guidelines are not a substitute to formal training programmes, which appropriate health staff would be expected to undergo. These guidelines are evidence based and draw upon various international guidelines and documents with an emphasis upon managing and treating those with opioid dependence in the Nigerian context.

In these guidelines, the term medication-assisted treatment (MAT) is used. The opioid agonists for these guidelines are methadone and buprenorphine. Not all countries or international institutions use the term MAT. Other terms used include opioid agonist maintenance treatment (OAMT), opioid agonist treatment (OAT) and opioid substitution therapy (OST). Medication-assisted treatment is widely used internationally and indicates the combined use of medication and psychosocial support.

1 UNODC. *Drug Use in Nigeria 2018*. UNODC, Vienna, Austria. 2018.

2 Federal Ministry of Health (FMOH). 2019. *National Guidelines for the Treatment of Substance Use Disorders for Nigeria*. FMOH and United Nations Office on Drugs and Crime, Abuja, Nigeria.

1.1 Substance use in Africa and Nigeria

Globally, of the 269 million people (aged 15–64) estimated to have used an illicit drug in 2017, an estimated 60 million were located in Africa. The number of people who use drugs (PWUD) in Africa is projected to rise in the next decade by as much as 40 per cent, largely due to demographic changes. The non-medical use of pharmaceutical opioids remains a major concern in many countries, including those in West Africa.³ A nationwide survey of drug users in Nigeria found that an estimated 14.3 million people (aged 15–64) had used an illicit drug in the previous year: 4.6 million used illicit prescription opioids, an estimated 87,000 used heroin, and among the approximate 376,000 high-risk PWUD (those who used opioids, crack/cocaine or amphetamines in previous 12 months, and had used at least five times in past 30 days), nearly 90 per cent were opioid users.

Among the high-risk PWUD, approximately 80,000 were PWID, with the majority injecting opioids (75 per cent). This survey found that 9 per cent of PWID reported that they were living with HIV, and it was highly likely these self-reported figures underrepresent actual prevalence. The national survey found that 12 per cent of those with high-risk drug use had ever received drug treatment, and only 4 per cent received drug treatment in the previous year.⁴ In 2018, the estimated national prevalence of HIV among the general population (aged 15–49 years) was 1.4 per cent but higher among PWID at 3.4 per cent, with HIV prevalence among female PWID about five times greater than among male PWID (13.9 per cent vs 2.6 per cent).^{5 6} It is against this background that rising illicit drug use in Nigeria remains a major concern.

1.2 Substance use disorders

Substance use disorders are a group of conditions related to consumption of alcohol or the use of other drugs such as cannabis, hallucinogens, inhalants, opioids, sedatives, amphetamine-type stimulants, cocaine, tobacco or unknown substances. Both *The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5), published by the American Psychiatric Association, and The World Health Organization's *International Classification of Diseases, 11th Revision* (ICD-11), recognize that people are not all automatically or equally vulnerable to developing substance-related disorders. Some people have high vulnerability that predisposes them to develop problems if they are exposed to drugs. Affected people feel a loss of control over their use of substances and continue regular and often heavy substance use despite health, legal and relationship problems. Opioid use problems (particularly dependence) are more common with regular use over long periods of time. However, not everyone who takes opioids, even long term, develops dependence.

3 UNODC. *The World Drug Report 2021*. UNODC, Vienna, Austria. 2021.

4 UNODC. *Drug Use in Nigeria 2018*. UNODC, Vienna, Austria. 2018.

5 Federal Ministry of Health. *Nigeria HIV/AIDS Indicator and Impact Survey*. 2018.

6 Federal Ministry of Health. *Integrated biological and behavioural surveillance survey*. Abuja: Federal Ministry of Health. 2014.

Substance dependence is a chronic relapsing medical condition, with complex sociological, psychological and biological components.⁷ Dependence on opioids is a serious condition, associated with severe morbidity, risk of transmission of blood-borne viruses especially related to the injection of drugs (HIV, viral hepatitis B and C) and death. These risks arise from drug overdose, and the morbidity and injury resulting from chronic illicit drug use, injecting or misuse of licit opioids.

WHY TREAT OPIOID DEPENDENCE?

In Nigeria, 4.7 per cent of the adult population was estimated in 2017 to be users of opioids. This places Nigeria among the countries globally with the highest rates of non-medical opioid use.⁸ As a consequence, the health, economic and social costs of opioid drug use are high due to:

- Death from fatal overdose: opioid-related deaths occur in younger people than do deaths associated with alcohol or tobacco.
- Medical and mental health consequences, including transmission of hepatitis B, hepatitis C and HIV, commonly linked to injecting opioids.
- Social consequences to individuals and their communities, including impacts on relationships, employment, education, housing, parenting, finances and crime.
- Costs to health and social services, law enforcement and judicial systems.⁹

Treatment of opioid dependence is a set of pharmacological and psychosocial interventions that can take place over different time frames, often requiring several attempts, multiple interventions and regular monitoring to ensure effectiveness. The major treatment intervention and therapies for recovery include: counselling; detoxification; abstinence-based treatments; residential and outpatient centres; support groups; and two separate pharmacological approaches, first for opioid withdrawal (detoxification) and then agonist maintenance. Agonist-maintenance treatment usually consists of daily administration of an opioid agonist (methadone) or a partial agonist (buprenorphine). Naltrexone is an opioid antagonist used in many countries. As of 2020, 84 countries around the world had at least one opioid agonist therapy programme, seven of which were found in Africa (Burkina Faso, Côte d'Ivoire, Kenya, Mauritius, Senegal, South Africa and Tanzania).¹⁰ The agonist treatments available and prescribed in Nigeria are methadone and buprenorphine.

7 Heilig, M., MacKillop, J., Martinez, D. et al. *Addiction as a brain disease revised: Why it still matters, and the need for consilience*. Neuropsychopharmacol. 2021.

8 UNODC. *Drug Use in Nigeria 2018*. Vienna, Austria. 2018.

9 WHO, UNODC, UNAIDS. *Substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention*. Geneva, Switzerland. 2004.

10 Harm Reduction International. *Global State of Harm Reduction 2020*. London, UK. 2020.

1.3 Methadone and buprenorphine: Effective treatment for opioid dependence

Methadone was first developed in Germany in 1941 for pain relief. In 1959, doctors in Vancouver, Canada began using methadone as a treatment for heroin dependence, followed in 1964 by doctors in New York, where it was demonstrated to be suitable as a maintenance treatment.¹¹ The use of buprenorphine for treating opioid dependence started in the 1980s. Methadone and buprenorphine are established in many countries as effective treatments for opioid dependence. Both medicines, administered as MAT, are effective evidence-based interventions, recommended by WHO and included on its Essential Medicines List and endorsed by other United Nations agencies to prevent the transmission of HIV and viral hepatitis among people who inject drugs and to treat opioid dependence.

Methadone has been prescribed for the treatment of opioid dependency for over five decades, and buprenorphine for more than three decades. Methadone and buprenorphine were added to the World Health Organization's List of Essential Medicines in 2005. Extensive international research has shown methadone and buprenorphine to be effective in the reduction of HIV risk behaviours and other comorbidities.^{12 13}

Methadone and buprenorphine can be compared to other drugs that are effective in the treatment of serious, chronic and relapsing conditions, such as hypertension and diabetes. These conditions, like opioid dependence, are chronic, require daily treatment and put patients at a high risk of suffering adverse effects if their compliance with treatment is poor.

The use of MAT means replacing the harmful opioid of dependence with another opioid that causes less harm. MAT is commonly taken in an oral form within a regulated environment under clinical supervision to prevent diversion, injection or the use of other opioid-based substances.

Relapse to heroin or other opioids following the cessation of methadone or buprenorphine treatment is common. However, long-term treatment, common for many medical conditions, should not be seen as treatment failure, but rather as a cost-effective way of prolonging life, improving quality of life, and supporting the natural and long-term process of change and recovery. Methadone and buprenorphine can prove valuable in assisting people to successfully manage physical dependence, cravings and compulsive drug use.

- 11 Defalque RJ, Wright AJ. *The early history of methadone. Myths and facts*. Bulletin of Anesthesia History. Oct;25(3):13-16. 2007.
- 12 Herget G. *Methadone and buprenorphine added to the WHO list of essential medicines*. HIV AIDS Policy Law Rev. Dec;10(3):23-4. 2005.
- 13 Lawrinson P, Ali R, Chiamwongpaet ABS, et al. *Key findings from the WHO collaborative study on substitution therapy for opioid dependence and HIV/AIDS*. Addiction. 103:1484-92. 2008.

Methadone is commonly prescribed for the following reasons:

- Its high cross-tolerance with other opioids (e.g., a person tolerant to a certain dose of heroin will also be tolerant to a dose-equivalent amount of methadone).
- Its less euphoric effect, so clients can avoid the reinforcing effect.
- It has good bioavailability by mouth and can be taken orally.
- It is slowly absorbed resulting in less intoxication and withdrawal symptoms.
- It is cheaper and preferable, particularly in patients with comorbid psychiatric issues, those less likely to adhere to therapy, those with comorbid chronic pain or pharmaceutical opioid dependence (e.g., codeine) and when the sedative properties of methadone may be of benefit.
- It is long-acting and needs to be taken just once a day.^{14 15}

Buprenorphine is commonly prescribed for the following reasons:

- It be preferable for higher-functioning individuals who need flexibility in dosing for employment purposes.
- It is less sedating than methadone.
- It is easier transition in and out of treatment with buprenorphine compared to methadone (this leads to greater patient flexibility but lower rates of retention in treatment).
- It can block the effects of other opioid agonists in a dose-dependent fashion.
- It is safer in high doses than full opioid agonists such as methadone.
- Induction with buprenorphine is usually safer and easier, with maintenance doses reached more quickly than with methadone.
- Its effect on respiratory depression reaches a ceiling, with higher doses not increasing respiratory depression to a significant degree. However, buprenorphine used in combination with other central nervous system depressants (e.g., benzodiazepines and alcohol) can be dangerous.^{16 17}

1.4 Major benefits of methadone and buprenorphine

A regular and routine supply of an adequate dose of methadone or buprenorphine in a supervised manner, as part of a structured programme, has demonstrated substantial benefits for the individual, their family and society. These benefits of MAT include:

- Reduced or limited non-medical opioid use.
- Reduced risk of opioid overdose.
- Reduced high-risk practice of sharing needles.

14 Gowing L., Ali R., Dunlop A., et al. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

15 WHO, Regional Office for South-East Asia. *Operational guidelines for the treatment of opioid dependence*. Delhi, India. 2008

16 Queensland Health. *Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines 2018*. Queensland, Australia. 2018.

17 WHO, Regional Office for South-East Asia. *Operational guidelines for the treatment of opioid dependence*. Delhi, India. 2008

- Decreased drug-related criminal activity.
- Reduced tendency to take drugs chaotically and improved life stability for patients.
- Improved quality of life.^{18 19}

Methadone and buprenorphine decrease the euphoric effects of other opioids (such as heroin) without necessarily causing euphoria or sedation for those who use this medicine. As a result, self-administered, non-medical opioids will not lead to euphoria, making it less likely that patients will continue to use non-medical opioids.²⁰

1.5 Settings for delivering MAT

Internationally, maintenance treatment with methadone and buprenorphine is delivered in a variety of settings, including:

- Substance use treatment centres/clinics (outpatient or inpatient)
- Hospital-based health clinics
- Mental health hospitals
- Pharmacies
- Medical practitioner clinics
- Community service organizations

Practitioners from different disciplines and backgrounds, including medicine, substance use treatment, nursing, social work and mental health, may be involved in programmes for delivering maintenance treatment with methadone or buprenorphine. Their roles vary, depending on factors such as qualifications, the setting of the programme, resources available and geographical location. It is recommended that those prescribing and dispensing methadone and buprenorphine receive training in medication-assisted treatment.

The goals of methadone and buprenorphine maintenance treatment include normalizing patients' lives, integrating them back into their families and communities, and keeping them in treatment when necessary.

1.6 Risks associated with methadone and buprenorphine programmes

Despite the proven success of methadone and buprenorphine programmes, the following risks should be noted:

- Methadone and buprenorphine are opioid drugs and as such, prone to misuse.
- Methadone is a potentially toxic drug with a low therapeutic index (the therapeutic dose is close to the toxic dose).
- Treatment with methadone or buprenorphine is provided to a high-risk population.

18 Ward J, Mattick R., Hall W, eds. *Methadone maintenance treatment and other opioid replacement therapies*. Amsterdam: Harwood Academic Publishers. 1998.

19 WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. 2009

20 Bart G. *Maintenance Medication for Opiate Addiction: The Foundation of Recovery*. Journal of Addictive Diseases, 31(3), 207–225. 2012.

Diversions can occur, most commonly in countries or places where patients receive a dose that is insufficient for their needs and/or where not enough people have access to MAT.

- Some patients have psychiatric and social problems. It is recommended that adequate treatment for patients with mental health or other comorbidities be provided.²¹

Despite the various risks of methadone and buprenorphine treatment, it is important to note that there are various countermeasures that can be taken to minimize risks, as outlined in **Appendix 2**.

1.7 Types of methadone and buprenorphine treatment

Withdrawal/Detoxication: Opioid withdrawal can be managed by controlling the rate of cessation of opioids and by providing medication that relieves symptoms, or by a combination of the two. Opioid withdrawal and detoxification services should be structured in such a way that withdrawal is not a stand-alone service but is integrated with ongoing treatment options, including psychosocial assistance.

Maintenance: A high proportion of patients who have withdrawn from opioid dependence will relapse. Research suggests that key treatment outcomes for buprenorphine and methadone maintenance treatment are comparable under optimal treatment conditions with high dosages for prolonged period of time. Overall, the difference between buprenorphine and methadone maintenance is minimal. It should be noted, however, that buprenorphine patients are significantly less likely to remain in treatment than methadone patients. Despite the slightly greater efficacy of high-dose methadone maintenance, many patients do well on buprenorphine.²² Generally, patients on methadone receiving a daily dose of 60 mg or more have better treatment outcomes than those receiving less than 60 mg. The recommended dose by WHO is between 60-120 mg. Generally, effective maintenance doses of buprenorphine, resulting in reduced heroin use and improved treatment retention, may be achieved with buprenorphine doses in the range of 8 to 24 mg/day.²³ A programme of maintenance on methadone or buprenorphine for prolonged periods will help these patients.

21 Queensland Health. *Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines 2018*. Queensland, Australia.

22 Mattick RP, Kimber J, Breen C, Davoli M. *Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence*. [Cochrane Review]. The Cochrane Library. Chichester, UK: John Wiley & Sons Ltd. 2003.

23 Gowing, L., Ali, R., Dunlop, A., Farrell, M., Lintzeris, N. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

Chapter 2

Clinical Pharmacology and Toxicology of Methadone and Buprenorphine



2. Methadone

Methadone is a synthetic opioid agonist that is well absorbed orally and has a long, although variable, plasma half-life. Methadone is available in several forms: injectable, oral solution and tablet. The oral solution form, usually administered as an oral liquid at 5 mg/mL, is recommended for the treatment of opioid dependence because when administered it is more easily supervised. Keep in mind:

- Methadone has a complex range of effects that can vary widely among individuals. It is used as a long-acting analgesic and a substitute treatment for opioid (mostly heroin) dependence.
- It is necessary to understand the pharmacology of methadone so that it can be used safely by patients with problems of compulsive drug use, often complicated by abuse of other drugs that depress the central nervous system (CNS).

The characteristics of methadone are as follows:

- A slow onset of peak blood levels (between two-and-a-half and four hours).
- Duration of effects (20-36 hours).
- Low therapeutic index (overlap of toxic and therapeutic blood levels).
- Acts by binding to the opioid receptors in the brain.
- Oral methadone is well absorbed from the gastrointestinal tract and is fat soluble. It undergoes extensive first-pass metabolism in the liver. It binds to albumin and other proteins in the lung, kidney, liver and spleen, and there is gradual equilibration between these tissues and blood over the first few days of dosing.
- Due to good oral bioavailability and long half-life, methadone is taken as a daily oral dose.
- Repeated dosing leads to accumulation.
- The risk of overdose is highest in the first few days of treatment when the ingested methadone equilibrates with tissue stores, as the patient stabilizes on methadone.^{24 25}

2.1. Buprenorphine

Buprenorphine is a partial opioid agonist, with actions similar to full agonist drugs but with less efficacy: the dose can be increased but progressively has less effect. A dose

24 WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. 2009
25 Gowing, L., Ali, R., Dunlop, A., Farrell, M., Lintzeris, N. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

that is increased beyond that which is required to saturate all receptor sites (usually 16 mg) will cause a prolonged duration of action, but the consumption of other opioids will have little or no further effect. Buprenorphine is available in three forms: film, tablet (both taken sublingually) and injectable.

The characteristics of buprenorphine pharmacology are as follows:

- Peak clinical effects occur between one to four hours after sublingual administration.
- Commonly, effects will continue to be experienced for up to 12 hours at low doses (2 mg), and as long as 48 to 72 hours at higher doses (16 or 32 mg).
- Prolonged duration of effects at high doses enables alternate-day and even three-days-a-week dispensing regimens.
- Buprenorphine is available as buprenorphine-mono (tablet) or as buprenorphine-naloxone 4:1 combination (sublingual). Naloxone is a non-selective, short-acting opioid receptor antagonist that is used for treatment of overdose. Naloxone is inactive orally, but when injected it attenuates the effects of buprenorphine and can precipitate withdrawal if the person is opioid dependent. Naloxone does not affect the absorption of buprenorphine.
- Buprenorphine, with a slow receptor dissociation and partial activity combined, results in a withdrawal syndrome that is milder than methadone.
- As a partial agonist, buprenorphine is safer than methadone with less risk of over-sedation, respiratory depression and overdose.^{26 27}

Onset and duration of response to methadone and buprenorphine

Onset and Duration	Methadone ²⁸	Buprenorphine ²⁹
Onset of effects	15-45 minutes (average)	30-60 minutes
Peak clinical effects	2.5-4 hours (average)	1-4 hours
Duration of effects	20-36 hours (average)	8-12 hours (low dose, e.g., 2 mg) 24-72 hours (high dose, e.g., >16 mg)

26 WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. 2009.

27 Gowing, L., Ali, R., Dunlop, A., Farrell, M., Lintzeris, N. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

28 Ibid.

29 Ibid.

2.2 Metabolism and drug interactions

2.2.1 Methadone

Methadone is largely metabolized by the cytochrome P450 enzyme CYP3A4, which is found primarily in the liver and in small quantities in the gastrointestinal mucosa. CYP3A4 inhibitors can decrease the metabolism of methadone and potentially cause overdose. CYP3A4 can include some macrolides such as erythromycin, SSRIs (particularly fluvoxamine), antifungals such as ketoconazole, and some HIV medications. Inducers (such as phenytoin, carbamazepine or rifampicin) can cause a withdrawal syndrome for patients on methadone. If possible, avoid prescribing. If a CYP450-inducing drug is clinically indicated for the treatment of another condition, specialist advice is recommended.³⁰

Renal clearance makes for a small proportion of the total clearance at a urine pH of 7. If the urine is acidic (pH below 6), then the proportion of renal clearance increases to about 30 per cent of the total clearance; if the urine is alkaline (pH above 7.8), renal clearance is reduced to zero. Patients should be advised on the use of urinary alkalinizers or acidifiers, including aspirin.

Approximately 10 per cent of methadone administered orally is eliminated unchanged. The rest is metabolized and the (mainly inactive) metabolites are excreted in the urine and faeces, as well as secreted in sweat and saliva.³¹

2.2.2 Buprenorphine

Buprenorphine is mostly metabolized in the liver by the cytochrome p450 system (CYP3A4) and glucuronidation. Most of the drug is excreted in the faeces and, to a lesser extent, in the urine. Buprenorphine undergoes extensive first pass metabolism in the small intestine and the liver when taken orally. Females exposed to the same doses of buprenorphine as males have higher blood concentrations of buprenorphine and active metabolites. The discrepancy is likely to be due to differences in body composition and is considered unlikely to be a major concern.³²

2.3 Interactions during pregnancy

2.3.1 Methadone

Methadone clearance increases during pregnancy, resulting in a corresponding decrease in plasma concentrations. This may increase the risk of the failure of treatment, self-medication and toxicity.³³ Pregnant women may benefit from split-dosing, taking smaller

30 Henry-Edwards, S., Gowing, L., White, J., Ali, R., Bell, J., Brough, R., Quigley, A., *Clinical Guidelines and Procedures for the Use of Methadone in the Maintenance Treatment of Opioid Dependence*. Canberra, Australia. 2003.

31 Ibid.

32 Queensland Health. *Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines 2018*. Queensland, Australia. 2018.

33 Wolff K, Boys A, Rostami-Hodjegan A, Hay A, Raistrick D. *Changes to methadone clearance during pregnancy*. Eur J Clin Pharmacol. 61(10):763-8. November, 2005.

doses more often, which reduces foetal exposure to withdrawal periods.³⁴ Given the variability of methadone clearance among pregnant women, they are regarded as a group that require close monitoring.

2.3.2 Buprenorphine

Pregnant women undergoing treatment for opioid use disorder with buprenorphine-naloxone do not experience significantly different pregnancy outcomes than women undergoing treatment with other forms of opioid agonist medication-assisted therapy such as buprenorphine-mono or methadone.³⁵ Increase in dosages may be required throughout the pregnancy, especially during the second and third trimesters.^{36 37}

2.4 Pharmacokinetic drug interactions

2.4.1 Methadone

There is potential for pharmacokinetic interactions between methadone and drugs that inhibit or induce methadone metabolism by CYP450 enzymes, predominantly CYP3A4.³⁸

Potential inhibitors of methadone metabolism are as follows:

- Selective Serotonin Reuptake Inhibitors - SSRIs (sertraline, fluvoxamine, etc.).
- Serotonin Norepinephrine Reuptake Inhibitors - SNRIs (venlafaxine, nefazodone).
- Broad-spectrum antifungals and antibacterials (erythromycin, ciprofloxacin, chloramphenicol clotrimazole, etc.).
- Antiretroviral drugs (zidovudine, ritonavir, etc.) (See **Appendix 3**).
- Hormones/steroids (progesterone, ethinylestradiol, dexamethasone).
- Calcium Channel Antagonists (nifedipine, verapamil, diltiazem).
- Miscellaneous (quinidine, midazolam, cyclosporin, vinblastine, bromocriptine, cimetidine).

2.4.2 Buprenorphine

Buprenorphine is a strong inhibitor of CYP-3A4 and CYP2D6. It has been reported that clinically this has little effect due to the low levels of buprenorphine required in therapeutic dosing.³⁹ However, it has also been reported that precaution should be exercised when buprenorphine is administered with CYP3A4 inhibitors (e.g., protease inhibitors, some drugs in the class of azole antimycotics such as ketoconazole, calcium channel

34 NIDA. 2017, July 1. Treating Opioid Use Disorder During Pregnancy. Retrieved from <https://www.drugabuse.gov/publications/treating-opioid-use-disorder-during-pregnancy> on July 22, 2021.

35 Link HM, Jones H, Miller L, Kaltenbach K, Seligman N. *Buprenorphine-naloxone use in pregnancy: a systematic review and metaanalysis*. Am J Obstet Gynecol MFM. 2(3):100179. August, 2020.

36 Winklbaur, B., Kopf, N., Ebner, N., Jung, E., Thau, K., and Fischer, G. *Treating pregnant women dependent of opioids is not the same as treating pregnancy and opioid dependence: A knowledge syntheses for better treatment for women and neonates*. Addiction. 103: p. 1429-1440. 2008.

37 Winklbaur, B., Jung, E., and Fischer, G. *Opioid dependence and pregnancy*. Current opinion in psychiatry. 21(3): p. 255-259. 2008.

38 Ferrari A, Coccia CP, Bertolini A, Sternieri E. *Methadone-metabolism, pharmacokinetics and interactions*. Pharmacol Res. 50(6):551-9. December, 2004.

39 WHO, Regional Office for South-East Asia. *Operational guidelines for the treatment of opioid dependence*. Delhi, India. 2008.

antagonists such as nifedipine, and some antiviral medications such as atazanavir) as this may lead to increased plasma concentrations of buprenorphine.⁴⁰

2.5 Potential inducers/inhibitors of metabolism

2.5.1 Methadone

Some anti-epileptic and anti-convulsant drugs (phenobarbitone, phenytoin, primidone and carbamazepine, but not valproate or benzodiazepines) and HIV drugs (nevirapine [Figure 1] and efavirenz) may induce methadone metabolism. For more information on glucocorticoids and anti-tuberculosis drugs (rifampicin and rifabutin), refer to **Appendix 3**.

There are other drugs that induce or inhibit enzymes that affect methadone metabolism. Alcohol and tobacco smoke are common inducers, and the common inhibitors include allopurinol, dextropropoxyphene, disulfuram, isoniazid and enoxacin. During induction into treatment with methadone, one should avoid commencing any drug that inhibits or induces the activity of CYP3A4. When commencing methadone treatment in the case of patients who use medications that inhibit CYP3A4, one should prescribe conservative doses of methadone, review the patient carefully for signs of toxicity during induction, and advise the patient about the potential for drug interaction.⁴¹

2.5.2 Buprenorphine

Buprenorphine is metabolized primarily through the cytochrome P450 pathway, and as a result it could interact with medications that induce or inhibit this pathway. Physicians should closely monitor patients taking the following medications. Inducers include: carbamazepine (Tegretol), phenytoin (Dilantin), phenobarbital, reverse transcriptase inhibitors and rifampin (Rifadin). Inhibitors include: azole antifungals, macrolide antibiotics and protease inhibitors. Note that cytochrome P450 inhibitors increase the effect of buprenorphine, whereas cytochrome P450 inducers decrease the effect.⁴² Such interactions are probably seldom of clinical significance.

2.6 Pharmacodynamic drug interactions of methadone and buprenorphine

Almost all methadone or buprenorphine-related deaths occur if the patient is on other CNS depressants, and patients who abuse or depend on other drugs may be at greater risk of methadone or buprenorphine toxicity. Types of drugs that have the potential for adverse effects with methadone or buprenorphine are as follows:

- Opioids are CNS depressants and may increase the risk of respiratory depression and overdose when used with methadone.

40 Mc Cance-Katz, E.E. *Drug-drug interactions in opioid therapy: A focus on buprenorphine and methadone*. PCM Scientific: London, England. 2015.

41 Department of Health, Ministry of Health, The Republic of the Union of Myanmar. *Guidelines on Methadone Therapy in Myanmar (3rd edition)*. 2019.

42 Donaher PA, Welsh C. *Managing opioid addiction with buprenorphine*. Am Fam Physician. 1;73(9):1573-8. PMID: 16719249. May, 2006.

- Benzodiazepines can cause respiratory depression on their own. They may increase the risk of respiratory depression when methadone is being used.
- Unlike methadone, the effect of buprenorphine on respiratory depression reaches a ceiling. This action makes buprenorphine safer than methadone in overdose. However, even low doses of buprenorphine can be toxic when combined with sedatives such as benzodiazepines and alcohol.
- Alcohol is a CNS depressant that is capable of causing respiratory depression and death. The combination of non-fatal doses of alcohol and methadone may cause fatal toxicity.
- High doses of tricyclic antidepressants (TCAs) can cause respiratory depression and pulmonary oedema, and these drugs may interact with methadone and increase the risk of toxicity. One must assess patients on TCAs for the risk of suicide and review them carefully for signs of toxicity during induction into treatment.
- Anti-convulsants: Phenytoin, carbamazepine and phenobarbital are all significant inducers of CYP3A4 and have all resulted in withdrawal symptoms in patients on methadone.^{43 44}

2.7 Side effects and precautions associated with methadone and buprenorphine

The side effects of methadone and buprenorphine are similar to those of other opioid analgesics (dependence, nausea, vomiting, constipation, respiratory depression and potential coma). Patients develop tolerance to most of these effects after long-term use. However, the pharmacology of methadone differs from that of most other opioids in the following ways: there is a long interval between ingestion and the time that it reaches the peak level in the blood; it has a long half-life, which varies considerably from individual to individual; it has considerable tissue distribution; and there is accumulation after successive doses.⁴⁵

Buprenorphine may precipitate opioid withdrawal symptoms one to four hours after the first dose. Buprenorphine displaces agonists from opioid receptors and, in the short term, may not produce sufficient agonist effects to compensate for the displaced opioid. This produces a withdrawal effect as the buprenorphine reaches its peak effects. However, this can largely be avoided by using appropriate dose induction procedures.⁴⁶ Refer to **Chapter 4** for induction doses.

2.7.1 Pharmacokinetic factors specific for methadone

These are relevant in the context of side effects and the safe prescription of methadone.

- Peak plasma concentration occurs two-and-a-half to four hours after oral dosing.

43 Henry-Edwards S, Gowing L, White J, et al. *Clinical Guidelines and Procedures for the Use of Methadone in the Maintenance Treatment of Opioid Dependence*. Canberra, Australia. 2003.

44 Gowing, L., Ali, R., Dunlop, A., Farrell, M., Lintzeris, N. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

45 WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. 2009.

46 NSW Clinical Guidelines: *Treatment of Opioid Dependence*. Sydney, Australia. 2018.

- Metabolism to inactive metabolites occurs in the liver, so before prescribing, consider whether the patient's liver function is impaired.
- The elimination half-life varies considerably (with a range of 15–60 hours).
- Plasma concentration varies greatly among patients and wide fluctuations occur in individual patients. The dose should be adjusted carefully when the drug is administered repeatedly.⁴⁷

2.8 Contraindications to methadone or buprenorphine

- Hypersensitivity.
- A history of respiratory depression, especially with cyanosis and excessive bronchial secretions during acute asthma attacks (as with other opioids).
- Acute asthma or chest infection.
- Acute alcoholism, head injury and raised intracranial pressure.
- Treatment with monoamine oxidase inhibitors (MAO).
- Active ulcerative colitis or Crohn's disease.
- Decompensated liver disease (for example, cirrhosis with jaundice and ascites).
- Biliary and renal tract spasm.
- Inability to give informed consent.⁴⁸

2.8.1 Precautions

- Intoxicated or sedated patients.
- Severe hepatic/renal dysfunctions.
- Respiratory insufficiency.
- Psychosis.
- High-risk polydrug use.
- Significant concomitant medical problems.⁴⁹

47 Gowing, L., Ali, R., Dunlop, A., Farrell, M., Lintzeris, N. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

48 WHO, Regional Office for South-East Asia. *Operational guidelines for the treatment of opioid dependence*. Delhi, India. 2008.

49 Ibid.

Chapter 3

Assessment: Suitability for treatment and intake procedures



3. History: Assessing substance use, physical and mental states, and social issues

Assessing suitability for treatment should be carried out in a consistent manner with each patient so as to reduce error. An assessment can be completed by any trained clinical staff, but the diagnosis of opioid dependence should be made by a doctor.

3.1 Establishing the patient's identity

The patient's identity should be established to avoid dual dosing of the same person. There is a need to confirm that the patient is who they say they are. This may be done with a national identity card (such as a voter card, driver's licence or other nationally recognized identity card, if applicable). If this cannot be provided, a family member, guardian or close contact of the patient can show their national identify card, along with an attestation of the patient's identity. Alternatively, if the patient cannot provide proof of identity, the doctor qualified to offer methadone or buprenorphine should consider creating an identity card for the purposes of treatment. In some countries, staff at treatment facilities have found it useful to have six copies of a recent photograph of the patient: to be attached to the medical records, registration card and prescription card at the dosing point, and the others to be kept in reserve for possible future transfers if necessary or for other needs. In other countries the health-care provider and patient agree on a personal code to be used for patient identification.

In Nigeria, another recommended means of identification is to use the already operational Nigerian Epidemiology Network of Drug Use (NENDU) for all patients, whether they are already in the treatment system or not. NENDU collects information associated with drug use from those accessing drug treatment in selected centres. If a patient is being registered for the first time for MAT, that data will be collected and stored in NENDU. If the patient is already in the treatment system, the person will provide their unique identification code. The unique identification code does not determine whether the person receives services or not, but that information should be collected. The 12-digit identification code is based on the patient's personal information as follows:

- First two letters of the surname (two characters)
- First two letters of the first name (two characters) – for women use the first two letters of the maiden name
- Year of birth (YYYY) (four characters)
- Sex (M or F) (one character)
- First three letters of the place (town/village) of birth (three characters)

3.2 Establishing an effective therapeutic relationship

Establishing a strong therapeutic relationship with the patient is crucial to effective treatment because many PWUD are uncomfortable while giving a history of their drug dependence. To build a trusting rapport, the doctor and treatment staff should display empathy, sensitivity and warmth towards the patient and treat them with dignity while being cognizant of cultural contexts. Developing rapport based on mutual respect, knowledge and the willingness to work through issues in a systematic fashion is critically important.

3.3 Assessing suitability and reason for treatment

A comprehensive substance use history is essential for assessing suitability and reason for treatment. Assess all types of drugs used (including non-medical and pharmaceutical opioids, alcohol, cannabis, stimulants, benzodiazepines), duration of use, quantity and frequency of recent use, route of administration, and time of last use. Enquire about previous drug treatment episodes attempts, including their perspective on what worked before, possible triggers leading to relapse, and treatment options considered by the patient at the time of the assessment. It is important to explore with the individual the reasons for seeking treatment as this will impact treatment goals, and will help determine if treatment is acceptable and appropriate for the patient.

Key areas of assessment⁵⁰

HISTORY	KEY COMPONENTS
a. Current and past drug and alcohol use	<ul style="list-style-type: none"> » Type of drug(s) (opioids, amphetamines, benzodiazepines, alcohol, other commonly used drugs locally) » Age at first use » Age at daily use » Current use amount/frequency » Age at first injection » Current and past treatment
b. Mental health conditions	Past episodes current and past treatment: <ul style="list-style-type: none"> – Depression – Anxiety – Mania – Psychosis – Self-harm
c. Comorbid medical conditions	<ul style="list-style-type: none"> » Viral hepatitis and chronic liver disease » Injecting-related injury and disease » HIV infection » TB

50 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

HISTORY	KEY COMPONENTS
d. Psychosocial issues	<ul style="list-style-type: none"> » 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 comorbidities	Psychiatric disorders, substance use-related disorders

A comprehensive medical history is the most important component of the assessment, and beneficial insights are dependent on an open dialogue between patient and doctor.

3.4 Previous treatment for substance use

The patient's account of previous treatment and relapse can provide valuable information in determining appropriate treatment and preventing relapses in the future. It can also provide an insight into the patient's reasons for requesting treatment. If possible, it is advisable to verify the information given by the patient with others that may have assisted in earlier treatment.

3.5 Psychiatric and medical comorbidity

It can sometimes be difficult to establish whether opioid dependence is causing or exacerbating mood disturbance, or vice versa. Assessment of the patient may reveal that withdrawal from other substances (such as methamphetamine or alcohol) and sedatives (such as benzodiazepine) may be associated with psychiatric problems. Many patients seeking methadone or buprenorphine maintenance therapy to resolve substance abuse problems have pre-existing psychiatric conditions (including psychosis) or mood disorders, such as depression and anxiety disorders.

3.6 Brief interventions during assessment

Brief interventions as a response to address the issues associated with opioid dependence may help patients understand that their substance use is putting them at risk and encourage them to reduce the risks associated with their substance use. Brief interventions can be conducted on any relevant topic during the initial assessment of the patient. The major areas in which brief interventions are conducted are:

- Risky behaviours (sharing needles and syringes and unsafe sex: PWID can be informed about NSP and where to access clean needles and syringes, and can be provided with condoms).
- Polysubstance use (making the patient aware of the interactions between different drugs).
- Overdose (enabling patients to reduce the risk).

3.7 Diagnosing opioid dependence

Dependency on opioid use is a chronic physical and psychological state resulting from neuroadaptation to recurrent opioid use. Physiological tolerance develops, so the individual requires opioids to achieve a 'normal' physical and psychological state.

Methadone or buprenorphine treatment is usually appropriate for people who are dependent on opioids. When opioid use dependency is not present, methadone or buprenorphine treatment is *not* indicated.

According to the WHO *International Classification of Diseases* [ICD]-10, opioid dependence is present if three or more of the following have been experienced or exhibited at some time during the previous 12 months:⁵¹

1. A strong desire or compulsion to take opioids.
2. Difficulty controlling the urge to take opioids.
3. The development of opioid withdrawal syndrome upon giving up the opioid and relieving this by intentionally reusing opioids.
4. Tolerance to the effects of opioids.
5. Preference for taking opioids and neglecting other normal activities. Increased amounts of time spent on obtaining opioids or recovering from their effects.
6. Persistent use despite knowledge of the serious harmful consequences of opioids.

3.8 Patients' eligibility for methadone or buprenorphine

- Appropriate only for patients with opioid dependence, and who have made at least one serious attempt at withdrawal.
- Opioid dependent individuals (satisfying the criteria for opioid dependence as defined by ICD-10 or Opioid Use Disorder by DSM 5 – refer to **Appendix 4**).

⁵¹ WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. Geneva, Switzerland. 2009.

- A person who has the ability to access a methadone clinic on a daily basis or a buprenorphine clinic every other day or every third day, depending on buprenorphine dose.
- A person willing to undergo maintenance treatment with methadone or buprenorphine (providing informed consent for terms and conditions of treatment).

3.8.1 Patients' non-eligibility for methadone or buprenorphine

Individual patients should be closely assessed for any non-eligibility, determined by:

- Acutely psychotic PWUD are not eligible.
- Those who are dependent on alcohol, benzodiazepines, amphetamine-type stimulants (ATS) or cannabis alone are not eligible for methadone or buprenorphine treatment. However, it is important to note that polydrug use (for example use of opioids and other drugs) should not be a reason to disqualify patients from MAT. A comprehensive review of the patient should be conducted before determining non-eligibility.
- Patients with acute medical conditions (severe hepatic disease, acute alcohol intoxication, respiratory illness or head injury) are not eligible.

Generally, the patient should be 18 years of age or older. However, there needs to be flexibility with respect to the age of the person who is using drugs and determining the patient's eligibility is ultimately up to the doctor. For those under 18 years, consent will need to be obtained from a parent, guardian or social welfare service. It is extremely important to consider the risk behaviours and harmful opioid use of the patient. It should be kept in mind that the potential benefit to the individual's health and social functioning outweighs the potential disadvantage of methadone or buprenorphine treatment.

Note: *If there are any doubts about a patient's suitability for methadone or buprenorphine treatment, a second opinion may be sought from other medical doctors that have been trained in MAT.*

In general, patients with a diagnosis of opioid dependence are suitable for either maintenance substitution or withdrawal therapy using MAT. A psychosocial intervention alone may be undertaken when the patient does not wish to commence medication or when the harm resulting from the use of pharmacotherapy may be greater than the benefit. An example is a young person who uses an opioid intermittently and who is brought to a drug treatment service by the family for the first time. Chronic, opioid-dependent patients (e.g., after several years of dependence) will almost certainly need long-term substitution therapy.

3.9 Investigations

Urine drug screening is useful (if available and affordable) to corroborate patient history and establish recent opioid and other substance use. It is important to note that delays in obtaining results should not delay treatment initiation when the diagnosis can be clearly established. Examining for other conditions with drug use such as blood-borne viruses or liver disease should be undertaken as needed. These are best conducted after the patient is stabilized.

Laboratory Tests Recommended:

- STI screening.
- HIV testing and counselling.
- Screening for viral hepatitis.
- Pregnancy test.
- Urine drug screening if available and affordable.

Note on Laboratory Tests

It is not essential to perform any laboratory test before initiating methadone or buprenorphine for a patient. If the doctor has conducted a clinical examination and has not detected any significant finding, methadone or buprenorphine can be safely started. It is a good practice to conduct routine laboratory tests (such as full blood count, liver function tests and renal function tests) in the initial days of assessment and treatment as a 'baseline' test. When there are noted findings on physical examination, the relevant laboratory tests are warranted.

3.10 Providing information about treatment

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

Information should be provided to the patient in the following formats:

- Verbal discussions, including answering the patient's questions.
- Written information, such as pamphlets in local languages (consider level of literacy).
- Posters on the walls of the treatment centre providing messages on health promotion.

The prescriber should provide the following information to the patient:

- An explanation of the causes of opioid dependence.
- The occurrence of peak effects two to four hours after the administration of methadone; one to four hours for buprenorphine.
- The accumulation of methadone over time, which results in a greater effect after five days or more, even on a fixed dose; for buprenorphine it can be just a few days.
- The possibility that it may take two to eight weeks to establish a methadone maintenance dose that will satisfactorily substitute for the opioid on which the patient is dependent (because the equilibration of tissue and blood levels takes time).
- The high risk of drug overdose in the first 10 days of treatment (specific to methadone), the risks related to combining methadone or buprenorphine with the unsupervised use of other CNS depressant drugs (particularly benzodiazepines) and alcohol, and the special risk associated with binge drinking.
- The fact that some medications can induce or inhibit CYP3A4 enzyme activity on methadone concentrations.
- If appropriate, an explanation of interactions between methadone and TB medicines (rifampicin) and some HIV medicines (particularly nevirapine and efavirenz).

- The effects and side effects of methadone or buprenorphine.
- Conditions of participation in the methadone or buprenorphine programme.
- Patients who cannot read should be read their rights and obligations at the time they enter the programme.
- The addictive nature of methadone or buprenorphine, with an emphasis on the potential benefit to the individual's health and social functioning outweighing the potential disadvantage of methadone or buprenorphine treatment.
- The behaviour expected during the programme.
- The likely duration of the treatment, the benefits of which are maximized if the patient remains under treatment for at least 12 months.
- The length of time required to withdraw from methadone and the fact that the patient may experience slight discomfort during this period. The time needed to withdraw from buprenorphine is shorter.
- The causes of drug overdose, the high-risk situations associated with overdose, the symptoms and signs of overdose, and the action to be taken when overdose is suspected. The patient needs to inform family, friends and/or associates about the symptoms and signs of overdose, and about the urgency with which a response is required when they suspect an overdose.
- Mechanisms for resolving grievances between patients and those responsible for their treatment.
- Support, information and linkages with other services if required and available.
- Harm reduction (including how to prevent the transmission of blood-borne viruses – HIV, HBV and HCV – and how to inject safely, as well as where to get safe injecting equipment, for example, from nearby needle and syringe programmes).^{52 53}

Methadone and buprenorphine may affect the capacity of patients to drive or operate machinery during the early stages of treatment, after an increase in dose or when patients are also taking other drugs. Warn patients about this effect before entry into treatment, when the dose of methadone or buprenorphine is increased or when the use of other drugs is suspected.

3.11 Options for treatment and treatment plan

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

52 Ministry of Health The Republic of the Union of Myanmar. *Guidelines on Methadone Therapy in Myanmar (3rd edition)*. The Republic of the Union of Myanmar. 2019.

53 Gowing, L., Ali, R., Dunlop, A., Farrell, M., Lintzeris, N. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

Drug dependency treatment planning should:

- Be a continuous process.
- Involve the patient and consider the patient's circumstances and case complexity.
- Involve other service or care providers to address their needs.

3.12 Psychosocial or pharmacological treatment

Psychosocial treatment is generally recommended as an adjunct to pharmacotherapy. If a patient is to be given psychosocial treatment alone, it is important to ensure that they have strong social support from family or close friends.

3.13 Maintenance versus opioid withdrawal

Most patients presenting for treatment of opioid dependence request withdrawal therapy in the false belief that when they have completed withdrawal they will be “drug free” and be 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 if they prefer this option:

- It supports the patient in the decision to seek treatment.
- It maintains engagement.
- It reduces opioid use.
- It allows the patient to remain abstinent.
- It helps to stabilize people for the commencement of ART, hepatitis C or TB treatment and improves their health status.
- It allows the patient to be provided with information about the high risk of relapse and related harms (such as overdose or allergic infection) when aiming for detoxification therapy.

3.14 Opioid withdrawal/detoxification management

Opioid withdrawal is rarely life threatening. However, pharmacologically assisted management of opioid withdrawal can make withdrawal from opioids more comfortable and more likely to succeed. The severity of opioid withdrawal depends on the dose and pharmacological properties of the opioids used. For example, untreated heroin withdrawal typically reaches its peak 36–72 hours after the last dose, and symptoms will have subsided substantially after five days. Symptoms and signs of opioid withdrawal and assessment of withdrawal severity are wide ranging.

Opioid withdrawal can be managed by controlling the rate of cessation of opioids and by providing medication that relieves symptoms, or by a combination of the two. For the management of opioid withdrawal, tapered doses of opioid agonists should generally be used, although alpha-2 adrenergic agonists may also be used. The use of methadone or buprenorphine is recommended in the management of opioid withdrawal. The duration of the dose taper should be at least three days; for methadone, a taper of ten days results in acceptable withdrawal symptoms during treatment and minimal rebound withdrawal

symptoms on cessation of the opioid agonist. Psychosocial services should also be routinely offered in combination with pharmacological treatment of opioid withdrawal.⁵⁴

Patients may unsuccessfully attempt withdrawal several times before embarking on substitution therapy. MAT is more successful than withdrawal therapy in reducing illicit opioid use and retaining patients in treatment. Most patients with a history of opioid dependence benefit from substitution therapy because it stabilizes their drug use and its consequences.

WHO Recommendations: Opioid withdrawal or detoxification⁵⁵

STANDARD RECOMMENDATIONS

- » For the management of opioid withdrawal, tapered doses of opioid agonists (methadone or buprenorphine) over one to two weeks should preferably be used, although alpha-2 adrenergic agonists may also be used (lower doses of clonidine or lofexidine).
- » Clinicians should not routinely use the combination of opioid antagonists and minimal sedation in the management of opioid withdrawal.
- » Psychosocial services should be routinely offered in combination with pharmacological treatment of opioid withdrawal.

STRONG RECOMMENDATIONS

- » Clinicians should not use the combination of opioid antagonists with heavy sedation in the management of opioid withdrawal.

3.15 Management of tramadol, codeine and pentazocine dependence

Although tramadol, codeine and pentazocine have the potential to lead to dependency, these drugs can commonly be considered lower potency opioids. However, there is increasing evidence that tramadol dependence can occur when used daily for more than a few weeks or months.⁵⁶ Recent reports have found that tramadol – dosage-related – led to a similar dependence profile as morphine and other opioids.⁵⁷ Withdrawal symptoms have been reported to mimic symptoms of opioid withdrawal, including abdominal cramps, anxiety, goose pimples, lacrimation, rhinorrhea, sweating and depression. First-line treatment for tramadol, codeine and pentazocine dependence is normally

54 WHO and UNODC. *International standards for the treatment of drug use disorders: revised edition incorporating results of field-testing*. Geneva, Switzerland. 2020.

55 WHO and UNODC. *International standards for the treatment of drug use disorders*. Geneva. 2016. World Health Organisation MH–GAP Intervention guide. Version 2.

56 WHO . Tramadol Update Review Report Agenda item 6.1 Expert Committee on Drug Dependence. 36th Meeting. Geneva. 16–20 June 2014.

57 UNODC. *At The Crossroads of Licit and Illicit: Tramadol and other pharmaceutical opioids trafficking in West Africa*. 2021.

detoxification and rehabilitation.⁵⁸ Clinical experience and neurobiological evidence indicate that opioid dependence is a chronic relapsing disorder. As a result, the majority of those with opioid dependency – including those dependent on tramadol, codeine and pentazocine – receiving drug treatment have a high likelihood of experiencing relapse.⁵⁹ A single relapse from tramadol, codeine or pentazocine dependence should not warrant commencement of MAT. Detoxification should generally be managed in the same way as other opioids, with initial dosages adjusted to take into account their lower potency profile. In some cases, tramadol withdrawal can result in atypical presentation, with symptoms related to its effect on serotonin and norepinephrine receptors. This can be associated with seizures and other symptoms of a severe serotonin syndrome. Patients withdrawing from tramadol during detoxification may require additional monitoring and treatment of symptoms as necessary.⁶⁰

The conditions that would warrant the use of MAT for tramadol dependency include the following:

- Previous detoxification and rehabilitation efforts that have failed (minimum of three failed attempts).
- Serious harms associated with ongoing injecting opioid use – injecting-associated harms (risks of blood borne viruses – HIV, hepatitis B and C viruses) and development of abscesses that potentially could lead to septicemia or limb amputation.
- Severe social, psychological (i.e., extreme restlessness, agitation or mood change) and other physical harms such as presence of seizures, convulsions, respiratory depression, abnormally low blood pressure, excessive energy and insomnia, to name just some consequences of use.

Information regarding the treatment of tramadol dependence with the use of MAT remains scarce. No specific guidelines are known to exist to manage tramadol dependence with MAT, but various research case studies have been conducted (with small sample sizes) to treat patients with tramadol dependence using buprenorphine-naloxone. Case studies using buprenorphine-mono or methadone maintenance to treat tramadol dependence were not found, though one case of detoxification from tramadol with methadone was found.⁶¹ The dose of buprenorphine-naloxone provided to patients was dependent on dose-related tramadol use. For high-dose tramadol use (1,200-1,500 mg per day), following induction, patients received buprenorphine-naloxone at doses of 32/8 mg daily.⁶² In similar earlier case reports, two patients with long histories of tramadol dependence had both been titrated to buprenorphine at a dose of 32 mg/naloxone 8 mg daily, after withdrawal. Both patients reported significant improvement in this treatment regimen,

58 Federal Ministry of Health (FMOH) and UNODC. *National Guidelines for the Treatment of Substance Use Disorders for Nigeria*. Abuja, Nigeria. 2019.

59 van den Brink W, Haasen C. *Evidence-Based Treatment of Opioid-Dependent Patients*. The Canadian Journal of Psychiatry. 51(10):635-646. doi:10.1177/070674370605101003. 2006.

60 Federal Ministry of Health (FMOH) and UNODC. *National Guidelines for the Treatment of Substance Use Disorders for Nigeria*. Abuja, Nigeria. 2019.

61 Leo RJ, Narendran R, DeGuiseppe B. *Methadone detoxification of tramadol dependence*. J Subst Abuse. Treat 19:297-9. 2000.

62 Jonathan I. Ritvo, Ryan Koonce, Christian C. Thurstone & Harvey L. Causey III. Letters to the Editor, American Journal on Addictions, 16:1, 67-68, DOI: 10.1080/10550490601080118. 2007.

weaning to lower doses, and achieving long-term tramadol sobriety.⁶³ Others have also recommended the use of buprenorphine-naloxone to treat tramadol dependence.^{64 65}

In Nigeria, those with sickle cell disease (SCD) were known to take pentazocine to treat chronic pain. For patients that are severely dependent on pentazocine, the first line of treatment would normally be detoxification and rehabilitation.

The use of MAT for pentazocine is warranted under following conditions and circumstances:

- Previous detoxification and rehabilitation efforts have failed (minimum of three failed attempts).
- Debilitating ulcers identified as a result of injecting pentazocine.
- Amputations resulting from complications of pentazocine use and other related adverse health consequences.

It has been reported that methadone should generally not be combined with partial agonists such as pentazocine because its administration affects only some of the pentazocine withdrawal symptoms.^{66 67}

Key Points

- » First-line treatment for tramadol, codeine and pentazocine is normally detoxification and rehabilitation.
- » Warranted use of MAT following three previous unsuccessful detoxification and rehabilitation efforts.
- » Serious social, physical and psychological harms associated with ongoing tramadol, codeine and pentazocine use can warrant MAT.

3.16 Patient consent and registration

Consent should be voluntary and should be obtained after the patient has been given an explanation about the risks, benefits and expectations of treatment. Ideally, information should be provided in both verbal and written forms, keeping in mind the patient's level of literacy. The written consent should be signed by the patient and dated.

Determination of a patient's decision-making capacity is an integral part of the initial assessment.

63 Ritvo JJ, Koonce R, Thurstone CC, Causey HL. *Tramadol dependence: treatment with buprenorphine/naloxone*. Am J Addict. 16(1):67-8. 5. 2007

64 Cupples N, Moore TA. *A case of tramadol dependence and successful treatment with buprenorphine/naloxone*. Ment Health Clin [Internet]. 3(6):283-5. Available from: <http://dx.doi.org/10.9740/mhc.n183348>. 2007.

65 Avula VC. *Effectiveness of buprenorphine in detoxification and naltrexone in relapse prevention of tramadol-dependent patients: A case series*. Arch Ment Health. 22:80-83. 2021.

66 WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. 2009.

67 Coman, Horia & Cozman, Doina. *The detoxification treatment for pentazocine addiction*. Psihiatru.ro. 54 (3). 18-20. 10.26416/Psih.54.3.2018.1913. 2018.

Consent for minors under the age of 18 years should be obtained from a parent or guardian. If this is not possible, before commencing treatment, the treatment team should involve social welfare agencies to identify an adult who can provide consent for the child.

Any person whose mental state impairs their capacity to provide informed consent (such as those with an acute psychotic illness or a severe affective disorder) should first receive adequate treatment for the psychiatric condition so that informed consent can be obtained before initiation of methadone or buprenorphine.

Treatment should not be commenced until the prescriber has registered the user and confirmed that they are not already receiving methadone or buprenorphine treatment from another site. A designated government-approved authority or department should also be notified at the time of commencement of methadone or buprenorphine treatment. A monthly summary report of new patients commenced on treatment should be maintained by a state and central authority.

Key principles for MAT⁶⁸

Retention in treatment: A patient on MAT and engaged in the use of illegal drugs should not be excluded from the programme. The preferred response should be to conduct a clinical adjustment of treatment. Medication dosage must never be adjusted as a reward or punishment for behaviour.

Safety: The safety of patients, staff and medication should always be central to the functioning of the programme. All patients require clear information on the rules and regulations within the centre.

Openness and flexibility: Minimize burdensome rules and regulations surrounding entry and retention in MAT for patients. Avoid long waiting times, limited dispensing hours and compulsory urine testing. Offering same-day treatment upon registration is a good practice. Encourage flexibility with operating hours for dispensing, particularly during specific religious festivals and events, public holidays, and for any genuine challenges experienced by patients.

Respect: Ensure that high-quality care for those receiving MAT is non-stigmatizing and non-discriminatory.

68 UNODC, International Network of People Who Use Drugs, UNAIDS, UNDP, UNPF, WHO, United States Agency for International Development. *Implementing comprehensive HIV and HCV programmes with people who inject drugs: practical guidance for collaborative interventions*. Vienna, Austria. 2017.

Chapter 4

Clinical practice of medication-assisted treatment



4. Methadone induction phase

Patients should be counselled not to consume opioids or sedatives (including alcohol) for 24 hours before the commencement of methadone treatment. While the first dose of methadone should not be delayed because of a patient's same-day use of heroin (or other opioids), the actual time of the first dose maybe postponed by an hour or two if there are signs of sedation. If a patient is intoxicated with heroin (or other opioids), the first (or any) dose of methadone should be delayed several hours and be administered with the higher risk faced by the patient in mind. The initial dose should be administered in the morning. The induction dose depends on:

- The severity of opioid dependence and the degree of recent tolerance to opioids.
- The use of other drugs, such as sedatives (benzodiazepines), and the misuse of alcohol.
- Concurrent medical conditions, including respiratory illness and impaired hepatic function.
- The time since the patient last used a drug and signs of withdrawal or intoxication.
- Anticipated interactions with other prescribed medication.
- Induction dose of methadone should be based on a careful assessment of the degree of neuroadaptation of the patient. Patients with low or uncertain degree of neuroadaptation should start on low doses of methadone and be closely observed.⁶⁹

Key objectives of the induction dose regimen are:

- Reduction of withdrawal symptoms.
- Reduction of cravings.
- Reduction of non-medical opioid and other drug use.
- Patient satisfaction and engagement in treatment.

The patient should be seen immediately before the initial dose of methadone to determine that they are not intoxicated and ensure safe dosage.

New patients should be dosed with caution. Initial doses are recommended to be between 5-20 mg. The initial dose should **never** exceed 30 mg.⁷⁰

The first dose of methadone is usually 15-20 mg. However, if there is doubt regarding the recent intake of opioids, the client can be started on a lower dose of 5-10 mg. Patients

69 WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. Geneva, Switzerland. 2009.

70 Ibid.

should be reviewed three to four hours after the first dose for signs of withdrawal or intoxication and this should inform adjustments in dosing during the first week of treatment. It is recommended that an additional 5–10 mg be given three to four hours after the induction dose if the Clinical Opiate Withdrawal Scale (COWS) tool (see **Appendix 5**) indicates moderate or severe withdrawal.

After the starting dose(s) on the first day, ensure that the patient spends three days on each dose before considering an increase in the dose, as it may take up to five days for a change in dose to have its full effect because of the long half-life of methadone.

The following table should guide prescribers in determining the initial dose of methadone:⁷¹

Induction initial dose	Situation/clinical condition
5–20 mg	In general, start low. The dose can always be increased. Prescribe this dose for people with low or uncertain levels of opioid dependence, high-risk polysubstance use, or with other severe medical conditions.
20–25 mg	Moderate level of opioid tolerance or some lower-level risk factor. Using opioids regularly for more than six months and using twice a day or more in the past two weeks.
25–30 mg	Higher level of opioid tolerance with minimal use of other drugs; patient well known to doctors with no special risk factors; prior methadone treatment with no special risk factors.

Patients should be reviewed three to four days after the first dose to determine whether the initial dose needs to be increased. A review enables the prescriber to determine the most effective dose and provides an opportunity for the management of the high risk of methadone or combined drug toxicity during induction. It also provides an opportunity to reinforce treatment education and to assess the patient for side effects. If the patient has been experiencing withdrawal symptoms for most of the period, the dose can be increased by a maximum of 10 mg.

DURING THE STABILIZATION PHASE, THE KEY PHRASE IS “START LOW – GO SLOW”.

⁷¹ Queensland Health. *Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines*. Brisbane, Australia. 2018.

The rate of increase should be individually assessed, and should generally not be greater than 10 mg every few days. The dose should be increased only after reviewing the patient and when clinically indicated. As a safeguard, the daily dose should not exceed 40 mg in the first seven days to avoid significantly exceeding opioid tolerance that could lead to risk of over-sedation and even fatal consequences.

4.1 Key points to be aware of during induction of methadone

- During induction, methadone can be sedating for some patients and can cause overdose if the dose is too high, particularly in those with low opioid tolerance, and in combination with other sedatives (such as benzodiazepines), or in those that may be experiencing hepatic failure linked to alcohol misuse or hepatitis B or C.
- The elimination half-life of methadone is typically in the range between 24 and 48 hours, but extremes on either side of this range have been found. Methadone accumulates in the plasma during induction. Patients should be told to expect increasing opioid effects after each dose during induction.
- Methadone has a delayed onset of action, with peak effects achieved two to four hours after dosing. Patients should be cautious and refrain from using other drugs (e.g., benzodiazepines or alcohol) during initiation of methadone treatment.⁷²

4.2 Establishing effective maintenance dose with methadone

As with the pharmacological treatment of other medical conditions, the dose is an important determinant of the effectiveness of treatment. Prescribing should not focus on reducing the dosage to a level that minimizes the risk of adverse effects or decreases dependence, but rather on effectively controlling the patient's craving for and continued use of non-medical opioids.

To establish effective maintenance dose with methadone, the following points should be noted:

- The maintenance dose should be individualized to the patient's needs.
- Evidence indicates that a maintenance dose of at least 60 mg per day is more effective than lower doses in achieving treatment outcomes such as decreased illicit drug use and better retention of patients in treatment.
- Reaching an effective maintenance dose usually takes two to three weeks, but for some individuals it may take up to eight weeks.

Methadone doses above 60 mg have better outcomes than lower doses. On average, it is recommended that methadone maintenance doses should be in the range of 60–120 mg per day. It is important that medical professionals prescribe effective doses of methadone. If patients are still using non-medical opioids, be prepared to increase the methadone dose.⁷³

72 WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. Geneva, Switzerland. 2009.

73 Ibid.

4.3 Flexibility with methadone maintenance dose

Establishing an effective maintenance dose requires a degree of flexibility. Some patients will be comfortable and tolerate 40 mg per day, while others will need considerably more. People living with HIV and receiving antiretroviral therapy are likely to require adjustments in the dose of methadone (commonly a higher dose will be required). Always ensure there is flexibility with methadone doses and provide treatment on a case-by-case basis.

Key Points

- » Counsel patients not to consume opioids or sedatives (including alcohol) for 24 hours before the commencement of methadone.
- » Initial dose administered in the morning. Should never exceed 30 mg.
- » Initial doses should be 5-20 mg.
- » Review three to four hours after the first dose for signs of withdrawal or intoxication.
- » COWS tool is useful to indicate moderate or severe withdrawal.
- » Patient spends three days on each dose before considering an increase in the dose.
- » During stabilization phase "start low – go slow".
- » Patient should refrain from using other drugs (e.g., benzodiazepines or alcohol) during initiation of methadone treatment.
- » Maintenance dose of at least 60 mg per day is more effective than lower doses in achieving treatment outcomes. Effective maintenance dose requires a degree of flexibility.

4.4 Buprenorphine induction phase

Unlike methadone, there is need for a precipitated withdrawal with buprenorphine. Patients should be counselled not to consume opioids within six hours (or if a person was prescribed methadone but was being shifted to buprenorphine, no opioids should be consumed within 24 hours) of the first dose of buprenorphine. Buprenorphine is a partial opioid agonist that 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. It is also possible for PWUD to return to non-medical opioids later that day to relieve the withdrawal symptoms. The partial agonist properties of buprenorphine allow for more rapid induction. Rapidly achieving an adequate dose of buprenorphine (usually within three days) is associated with an improved rate of retention in treatment.^{74 75}

74 World Health Organization, *Regional Office for South-East Asia. Operational guidelines for the treatment of opioid dependence*. Delhi, India. 2008

75 WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. Geneva, Switzerland. 2009.

It is recommended that patients be commenced on buprenorphine-naloxone film unless pregnant or breastfeeding, or with a proven allergy to naloxone. Buprenorphine-naloxone combination preparations are less likely to be injected than buprenorphine-mono. As a partial agonist, buprenorphine is safer than methadone with less risk of over-sedation, respiratory depression and overdose. For buprenorphine induction:

- Defer the first dose until the patient is experiencing mild to moderate withdrawal (anxiety, abdominal or joint pain, dilated pupils, sweating). The rating scale Clinical Opiate Withdrawal Scale (COWS) can be helpful.
- Provide an initial dose of 4 mg for the patient with mild withdrawal (subjective symptoms but no signs of opioid withdrawal that would produce a score less than 8 with the COWS), with the possibility of a subsequent dose of 4 mg after one to two hours ('split dosing' reduces the risk of precipitated withdrawal).
- Provide an initial dose of 8 mg for the patient with moderate or severe withdrawal at the time of the first dose.
- Lower doses (e.g., 2 or 4 mg total on day one) are suited to those with low or uncertain levels of opioid dependence, with high-risk polydrug use (alcohol, benzodiazepines) or with other severe medical complications. Seek specialist advice if concerned.
- The buprenorphine dose on subsequent days can be increased by 2, 4 or 8 mg with upper limits of 16 mg on day two and 24 mg on day three. Slower dose increments (as used for methadone) are not required, and indeed dose increments that are too slow are associated with higher rates of treatment drop-out.⁷⁶

Initial buprenorphine doses ⁷⁷

SITUATION	INITIAL DAILY DOSE
Clients with low or uncertain levels of opioid dependence, high-risk polysubstance use, or with other severe medical conditions.	2-4 mg.
Clients with mild opioid withdrawal. (Split-dosing reduces risk of precipitated withdrawals).	2-4 mg initial dose. Further supplementary dose after one to two hours, up to maximum 8 mg for first day.
Moderate to severe opioid withdrawal at time of first dose.	Up to 8 mg.

⁷⁶ Queensland Health. *Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines*. Brisbane, Australia. 2018.

⁷⁷ WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. Geneva, Switzerland. 2009.

4.5 Establishing effective maintenance dose with buprenorphine

Typically, a maintenance dose will be in the range of 8-24 mg per day. However, some patients require higher (up to 32 mg a day) or lower (4-8 mg a day) doses to achieve their treatment goals. This can generally be achieved well within the first week of treatment, subject to adherence to the treatment plan by the patient. When establishing effective maintenance dose with buprenorphine, note the following:

- Achieving an optimal dose with buprenorphine is simpler than with methadone.
- Patients are less likely to become intoxicated with buprenorphine because it only partially activates the opioid receptors.
- The maximum daily dose during therapy is 32 mg.
- The buprenorphine dose can be increased by 2, 4 or 8 mg daily, with upper limits of 16 mg on day two and 24 mg on day three. Adjust doses following review of the patient – assessing side effects, features of withdrawal (suggesting not enough buprenorphine) or intoxication (suggesting too much buprenorphine or other drug use), ongoing cravings and substance use.
- Dose increments that are too small are associated with higher rates of treatment drop-out.
- Buprenorphine has a long half-life and, as such, dosing can be less frequent than daily.
- Effect of higher dosing reaches a ceiling after which higher doses result in a longer duration of action. This does not happen with methadone.
- After initial dose and clinical stabilization, the medication can be given every two or three days depending on the dose received.⁷⁸

Key Points

- » With buprenorphine, there is need for a precipitated withdrawal.
- » Counsel patients not to consume opioids within six hours before buprenorphine induction.
- » Buprenorphine induction displaces other opioids from the receptor but only partially activates the receptor. This results in a precipitated relative withdrawal state that can be uncomfortable.
- » Partial agonist properties of buprenorphine allow for more rapid induction, with adequate dose usually within three days.
- » Typically, a maintenance dose will be in the range of 8-24 mg/day.
- » Maximum daily dose during therapy is 32 mg.
- » Buprenorphine has a long half-life: dosing can be less frequent than daily.

78 Gowing, L., Ali, R., Dunlop, A., Farrell, M., Lintzeris, N. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

4.6 Signs and symptoms of opioid withdrawal or intoxication

The two most important findings upon clinical assessment that guide dose changes when establishing maintenance are:

- » The presence of signs and symptoms of opioid withdrawal or intoxication.
- » The use of opioids for non-medical purposes.

Signs and symptoms of opioid withdrawal⁷⁹

- | | |
|------------------------|---------------------------------|
| » Dilation of pupils | » Lacrimation |
| » Anxiety | » Rhinorrhoea |
| » Muscle and bone ache | » Anorexia and abdominal cramps |
| » Muscle cramps | » Nausea |
| » Sleep disturbance | » Vomiting |
| » Sweating | » Diarrhoea |
| » Hot and cold flushes | » Palpitations |
| » Piloerection | » Rapid pulse |
| » Yawning | » Raised blood pressure |
| | » Increased bowel sounds |

Signs and symptoms of opioid intoxication⁸⁰

- » Constriction of pupils
- » Itching and scratching
- » Sedation and somnolence
- » Lowered blood pressure
- » Slowed pulse
- » Hypoventilation

The dose of methadone or buprenorphine 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 until non-medical opioid use is generally less than once a week.

In order to reduce the risk of overdose, doses of methadone should be increased by a maximum of 10 mg, with a gap of at least four days separating each dose increment. If there is evidence of intoxication following methadone, enquiries should be made about other drug use (particularly benzodiazepines) or alcohol and, if necessary, the methadone dose should be reduced by 5-10 mg.

⁷⁹ Ibid.

⁸⁰ Ibid.

4.7 Regular review of patient's progress on methadone and buprenorphine

4.7.1 Methadone

Patients should be reviewed regularly by the managing team. The team should discuss the patient's progress on at least two occasions in the first week of treatment, about two times per month for the second and third months, and monthly thereafter. Patients should be clinically reviewed on:

- Day one, four hours after the first dose.
- Day three or four.
- End of week one.
- At least once a week for the first month or until a stable dosage has been achieved.
- At least every two weeks for the first two and three months.
- At least monthly thereafter.⁸¹

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

4.7.2 Buprenorphine

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 one, four hours after the first dose.
- Day three – by this stage the likely stabilization dose should be reasonably clear.
- End of week one.
- 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.

If a patient's clinical condition deteriorates, revise the schedule. Each review should include the drug history, physical examination, mental state examination and modification of the management plan, if required.⁸²

With methadone and buprenorphine, the purpose of conducting a progress review is to gain a better understanding of the clinical and psychosocial issues affecting the patient, and develop a strong therapeutic relationship with them. Although patients are usually preoccupied with the length of treatment, emphasis should be placed on the importance of clinical and psychosocial progress in determining the duration of the treatment.

4.8 Risks of methadone toxicity: Signs and symptoms

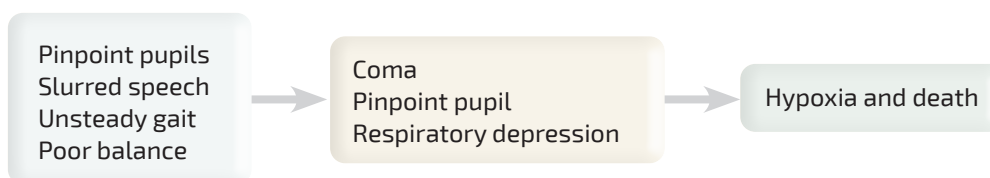
Some patients are at a greater risk of methadone toxicity than others, particularly during induction. The toxicity of methadone resembles that of other opioids: sedation, coma, respiratory depression and miosis (pinpoint pupils) can occur following an overdose.

81 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

82 Ibid.

However, the pharmacokinetics of methadone are unique, particularly the long interval between ingestion and the time that it reaches its maximum effect, and its long half-life (which results in tissue accumulation). Interaction with other CNS depressants can exacerbate the sedative effects of methadone. The risks of overdose and death are the highest in the first 10 days of treatment. This is because during this time, the patient may misuse other CNS depressants (including alcohol and benzodiazepines) or continue with non-medical drug use in an effort to minimize the withdrawal symptoms before becoming stabilized in treatment.⁸³

Methadone is a potentially toxic substance. Death occurs because of hypoxia due to respiratory depression, usually the result of interactions with other sedatives, of which benzodiazepines are the most common. Signs and symptoms of methadone toxicity are as follows:



This is a serious medical emergency. Urgent review by the prescriber is necessary.

It is not uncommon for methadone or buprenorphine to have various side effects. Patients should be educated on the potential side effects before commencement of treatment. This will allow for early detection and management. For key side effects, the common causes and suggested responses see **Appendix 6**.

The respiratory depression associated with an overdose of buprenorphine may be linked to the effects of alcohol or benzodiazepines. Treatment approach is found in Section 4.9.

4.9 Treatment of methadone or buprenorphine overdose

4.9.1 Methadone

The highest risk of drug overdose occurs in the first two weeks of treatment, when the ingested methadone is equilibrating with tissue reservoirs and accumulating in the body. The level of methadone in the blood during this period may not be sufficient to prevent craving, or may reach a toxic level if the clinical judgement regarding tolerance is incorrect. The patient may continue using illicit opioids or high doses of prescription drugs to self-manage the symptoms.

Patients who are on long-term methadone treatment and appear to be suffering from a methadone overdose can be observed for four to six hours at the dispensing centre. If there are no signs of toxicity, the patient can be discharged and asked to return the next day. Patients who are unaware of the effects of methadone or are experiencing a clinical

83 Department of Health, Ministry of Health, The Republic of the Union of Myanmar. *Guidelines on Methadone Therapy in Myanmar (3rd edition)*. 2019.

overdose of methadone, as described above, should be referred to the drug dependency treatment hospital.⁸⁴

A patient suffering from a methadone overdose should be treated as follows:

- Administer naloxone.
- Provide respiratory support – commence cardiopulmonary resuscitation. If no response: perform mouth-to-mouth resuscitation and chest compressions (30 compressions after every two breaths [ensure each breath lasts about one second and makes the chest rise] until breathing resumes).

4.9.2 Buprenorphine

Doses many times greater than normal therapeutic doses appear to be well-tolerated in most individuals. Rarely do they result in clinically-significant respiratory depression, except in individuals who are not opioid tolerant. However, if treatment of overdose is needed, it is more difficult because naloxone, an opioid antagonist that reverses opioid overdose, does not readily reverse the effects of buprenorphine. If respiratory depression occurs as a result of overdose, management in a hospital using ventilation is recommended, as well as an examination of the underlining causes.⁸⁵

4.10 Use of naloxone to treat overdose

Naloxone is an effective antidote to opioid overdose and will completely reverse the effects of an opioid overdose if administered in time. Naloxone can be delivered by intravenous, intramuscular, subcutaneous and intranasal routes of administration. The initial dose should be 0.4–2 mg, targeting recovery of breathing. In most cases 0.4–0.8 mg is an effective dose. It is important to provide sufficient naloxone to supplement the initial dose, as necessary. More than one dose may need to be available in a non-medical setting. Naloxone has virtually no effect in people who have not taken opioids. Naloxone cannot be used to get high, so it has no potential for misuse. There is no evidence that extended use of naloxone can cause harmful physical effects or dependence. People who take naloxone do not develop a tolerance to its effects and there have been no reported deaths from naloxone overdose.

People who have been revived with naloxone after overdosing on opioids may experience a strong urge to take more opioid drugs, especially if they are dependent on opioids. Naloxone only stays in the body for a short period of time (one to one-and-a-half hours) whereas heroin and other opioid drugs stay in the body for much longer. The effects of sustained-release opioids can last for over 12 hours, so naloxone will wear off long before the opioid has left the system. This means that taking more opioids after taking naloxone could cause a second overdose, and thus the person needs to be observed for one to two hours and monitored for another health crisis. People who are likely to witness an opioid overdose, including people who use opioids, and their family and friends should be given access to naloxone, and training in its use. This will allow them to respond to

84 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

85 Ibid.

opioid overdose in an emergency if a medical response is not available. WHO recommends community distribution of naloxone.^{86 87 88 89}

High risk for methadone toxicity is more likely in the following circumstances:

- Upon the patient's first presentation as a person who uses drugs, and their medical history and history of drug use are unclear.
- The patient has a high risk of polydrug abuse and dependence.
- The degree of neuro-adaptation is unclear.
- The patient has a risk of overdosing on methadone or any other drug.
- The patient has a clinically significant respiratory disease.
- The patient has a clinically significant liver disease.
- The patient uses drugs that inhibit CYP3A4 enzyme.

Methadone-related drug deaths due to methadone toxicity alone are rare: most cases (about 90 per cent) involve methadone use combined with prescription drugs and alcohol. Prescription drug misuse is common, and these drugs contribute to potentially dangerous toxicity, cognitive impairment and anterograde amnesia.

4.11 Counselling

Counselling may help the patient address their drug dependence problem. It is up to prescribers to choose whether they will counsel the patient themselves or whether to refer the patient to another counsellor. The patient's dispenser may also provide limited counselling. Patients with special counselling needs may need to attend a specialist drug treatment centre or consult a psychiatric service, if available and accessible. The other matters on which counselling should be provided are risk behaviours, the prevention of the transmission of blood-borne viruses (HIV and hepatitis B and C) and testing for these diseases.

4.12 Health staff

All organizations involved in drug treatment services that administer methadone and buprenorphine should be equipped with the following:

- Outpatient and inpatient managing staff who are engaged with methadone and buprenorphine programmes should be knowledgeable about national programme policy and guidelines.

86 World Health Organization. *Overdose: Community management of opioid overdose*. Geneva, Switzerland. 2014.

87 Fairbairn, Nadia et al. *Naloxone for heroin, prescription opioid, and illicitly made fentanyl overdoses: Challenges and innovations responding to a dynamic epidemic*. International Journal of Drug Policy, Volume 46, 172 – 179. 2017.

88 European Monitoring Centre for Drugs and Drug Addiction. *Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone*. EMCDDA Papers, Publications Office of the European Union, Luxembourg. 2015.

89 WHO. *Community management of opioid overdose*. Geneva, Switzerland. 2014.

- Trained and approved methadone and buprenorphine prescribers can commence patients on these medicines.
- Clearly documented and understood roles and responsibilities for managing staff.
- Proper recording and regular reporting (monthly), in keeping with the national guidelines.
- A senior consultant to monitor the management of methadone and buprenorphine therapy in a new drug treatment facility. This is to ensure uniformity of the reporting and recording of national data in line with the existing system.

4.13 Prescribing, dispensing and responsibility arrangements

Health professionals dispensing opioid pharmacotherapy to patients are an integral part of the managing team, particularly as frequent contact with patients facilitates the development of a good rapport. Physicians shall be responsible for proper filling in, signing and stamping of the controlled medicines prescription form for MAT. For registered pharmacists, it is their duty and responsibility to import, manufacture, procure, store, distribute, sell, compound and dispense controlled medicines and substances in accordance with extant rules and laws in Nigeria.

As outlined in the National Policy for Controlled Medicines, pharmacists shall ensure rational dispensing and use of controlled medicines, and take all appropriate steps to prevent diversion of controlled medicines and substances under their custody. At the facility level, the pharmacist in-charge shall be responsible for stocking narcotics and checking the prescription order, ensuring all the information is complete. If there is no nurse at the pharmacy, a trained pharmacist can also be responsible for administering of MAT to patients. At a clinic, the nurse-in-charge shall be responsible for keeping custody of narcotic medicines under lock and key in a designated cupboard or box. The nurse-in-charge of the clinic shall be responsible for direct administration of any controlled medicines to the patient, and maintain proper documentation of the medicines and their use.⁹⁰

4.14 Supervised dosing

Written instructions on dosing are to be documented in a patient's daily dispensing book, which is kept in the dispensary or clinic. The format of the daily dispensing book may vary across the sites dispensing methadone or buprenorphine. The dispensing book should contain the following details:

- Name and date of birth of the patient (or another identifier in the case of identical names).
- Patient's identification number.
- A photo may be useful, when available.
- Dates within which the prescription is valid.
- Dose in milligrams (mg).
- A record of each dose dispensed, signed by the dispenser.
- Space for ancillary notes about adverse events or situations.

90 Federal Ministry of Health, Nigeria. *National Policy for Controlled Medicines and its Implementations Strategies*. 2017.

The daily dispensing book is to be used at the methadone dispensing site to review the attendance of the patient, and changes in dose are to be noted directly on the prescription and in the dispensing books by the prescriber.

Patients receiving buprenorphine will have a dispensing book, but attendance will unlikely be daily – prolonged duration of effect at high doses means double (alternate-day dosing) or even triple (third-day dosing) dispensing regimens can be considered following stabilization.

4.15 Administration and supervision of doses until the patient has become stable

The nurse-in-charge of the MAT clinic shall be responsible for direct administration of any controlled medicines to the patient, and maintain proper documentation of the medicines and their use.⁹¹ Supervised doses should be directly observed during the *early phases of treatment*, until the patient has become stable. Observe the client throughout the dosing process, especially when the dose is placed in the mouth and immediately after. Once the dose is placed in the mouth, ensure that the patients' hands are kept away from their mouth. Both methadone and buprenorphine should be consumed in full view of the dispenser. With buprenorphine-mono or sublingual film, the medicine is placed under the tongue and the patient is advised not to chew or swallow until the medicine is fully dissolved. Sublingual film adheres to the sublingual mucosa within seconds once administered, and is difficult to remove after 30 to 60 seconds, making it difficult to divert the dose from the mouth. Under normal circumstances, supervision of a sublingual film dose does not need to exceed one minute. No remaining methadone or buprenorphine should be visible in the mouth of the patient before leaving a dispensing site. When the patient has become stable, take-home dosing is recommended.⁹²

4.16 Split-dosing

Split-dosing refers to twice-daily dosing. A small minority of patients may benefit from split-dosing. It can be considered for patients who are rapid metabolizers of methadone due to genetic variation or interaction with medications (for example ART-efavirenz) that induce CYP 450 enzymes. In these cases, split-dosing is more beneficial than higher doses administered once a day. It is considered appropriate and more common for women in the third trimester of pregnancy. While dispensing split-doses, the morning dose is usually administered under supervision and the afternoon dose is taken at home. In cases in which a take-home dose is not safe, both doses should be administered under supervision. Safety issues, such as diversion of doses and use of other drugs, must be considered prior to authorizing split-dosing. A second opinion or specialist referral is commonly recommended for split-dosing.⁹³

91 Federal Ministry of Health, Nigeria. *National Policy for Controlled Medicines and its Implementations Strategies*. 2017.

92 WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. Geneva, Switzerland. 2009.

93 Department of Health, Ministry of Health, The Republic of the Union of Myanmar. *Guidelines on Methadone Therapy in Myanmar (3rd edition)*. 2019.

Split-dosing generally does not apply to buprenorphine, although on rare occasions (such as a client with severe acute pain), a prescriber will approve a brief period of interval doses throughout the day.

4.17 Take-away (take-home) doses

Despite the risks, incidents of misuse and adverse consequences arising from take-away doses are generally not common, except for buprenorphine-mono, where reports of injecting the drug have been found. It is recommended that when patients are stable, take-away doses be provided. Methadone and buprenorphine are strictly controlled medicines. People with a history of substance use *may* misuse it by mixing it with other psychoactive drugs, such as benzodiazepines and/or alcohol. Drug-dependent friends or partners may steal a patient's take-away dose. This has been known to cause deaths. Children are particularly vulnerable to overdose, calling for special care in the safe storage of methadone and buprenorphine.

Take-home doses of buprenorphine-mono 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 and may be considered after a continuous period of stability in treatment. Patients on supervised buprenorphine-based therapy can be dosed as infrequently as three times a week using double and triple doses.

The provision of take-away doses may offer the following positive results:

- Improve patients' reintegration into normal daily activities and routines and their ability to meet work and family commitments by reducing the inconvenience of regular attendance at MAT clinics.
- Reduce the cost and time spent travelling to MAT clinics.
- Enhance treatment outcomes, in which positive behaviours (such as regular attendance for appointments) are linked to increased access to take-away doses.
- Improve patient autonomy in the management of their medication and treatment in general. This is consistent with the principles of chronic disease management such as HIV.
- Reduce stigma associated with routinely attending MAT clinics, particularly among patients concerned in maintaining confidentiality.
- Assist in the management of a chronic medical condition as well as in situations such as court appearances, visiting distant sick relatives, holidays or conferences, etc.
- Contribute to compliance with prolonged methadone maintenance and the retention of patients in treatment.⁹⁴

Take-home medication should be identical in dose to supervised doses. The patient should be assessed for stability before take-home dosing is commenced. It is important to note for patient that have been on methadone for less than three months and for those on

94 Gowing L., Ali R., Dunlop A., et al. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

buprenorphine-naloxone less than two weeks, take-home dosing is not recommended. However, this timeframe may be lowered for patients who live in rural areas. See 4.18 for take-home dosing for patients in rural areas.

The assessment of a patient's stability should take the following criteria into account:

- Current adherence to supervised dosing.
- Current adherence to appointments with the management team.
- No evidence of recent intoxicated presentations or overdoses (e.g., in previous three months for methadone).
- Recent pattern of methadone or buprenorphine use has been in accordance with prescription (no missed doses).
- Stability of mental health.
- Stability of accommodation.
- The availability of a secure area to store medication (particularly if there are children at home).
- Little evidence of intention to divert or inject take-home doses.⁹⁵

There is a need to strike a balance between risk management and patient autonomy with take-away doses. Risks to others and the community in general need to be considered. It may be difficult to assess the suitability of a patient for take-home dosing. The entire treatment team, including the dispenser, must take the decision in consultation with each other.

A suggested tool to further assess an individual patient's relative risk and suitability for take-home dosing is found in **Appendix 7**.

4.18 Take-home dosing for patients in rural areas

For patients treated for opioid dependence in rural areas, attending daily supervised dosing is likely to be a challenge. Under these circumstances, 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 or small town should be done with the supervision of the local village or small-town health worker or 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. When a patient has been stable for a longer period of time or the village or small-town health worker or 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 MAT.⁹⁶

95 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

96 Ibid.

4.19 Safety of take away (take-home) dose

Methadone and buprenorphine-mono can cause harm and result in fatal drug overdose (less fatal with buprenorphine-naloxone) if consumed inappropriately or by a person for whom it is not prescribed. It is important that take-home doses be in a locked box or cupboard so as not to cause harm or be misused by others. Staff responsible for dispensing take-home doses must emphasize the importance of the safe storage of methadone or buprenorphine-naloxone to the patient, their family or significant others. Information should be conveyed verbally and in writing. Here are some rules for patients to abide by:

- Keep the key to the box or cupboard where methadone or buprenorphine-naloxone is stored in a safe place.
- Keep the key to the lock box out of reach of children.
- Take the methadone or buprenorphine-naloxone as prescribed and then put it away.
- Never leave an opened bottle of methadone unattended.
- Never leave take-away doses where someone else can see or access them (e.g., not in the fridge, in a bag, on a shelf or table).
- Rinse out the cup used to drink methadone.
- Return empty bottles of methadone to the locked box or cupboard. Do not throw away empty bottles.
- Do not put methadone in bottles other than their original ones provided by the MAT clinic.
- Patients should talk to their family or significant others about the dangers of methadone or buprenorphine-naloxone and the importance of maintaining the medicine safely.
- Methadone container provided by dispenser should be child proof.^{97 98}

4.20 Steps for prescriber-authorized take-away (take-home) doses

Methadone

Incremental steps for take-away dosing might progress as follows:

- No take-home doses in the **first three months** of treatment.
- Assess stability and family support.
- 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.
- Assess stability over one month – should not be more than four days per week.⁹⁹

97 Department of Health, Ministry of Health, The Republic of the Union of Myanmar. *Guidelines on Methadone Therapy in Myanmar (3rd edition)*. 2019.

98 State of Victoria, Department of Health and Human Services. *Policy for maintenance pharmacotherapy for opioid dependence*. Melbourne, Australia. 2016.

99 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

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. However, if the entire managing team, including the dispenser, is fully convinced of the stability criteria of the patient, take-away dose of up to seven days should be permitted in circumstances such as travel, family and employment commitments.

Buprenorphine-naloxone

Supply of take-away doses may be considered after a continuous period of stability in treatment. The following schedule is recommended:¹⁰⁰

< 2 WEEKS	No take-away doses
2 WEEKS-2 MONTHS	0-2 take-away doses per week
2 MONTHS-6 MONTHS	0-5 take-away doses per week
> 6 MONTHS	0-6 take-away doses per week

4.21 Risk management and patient autonomy

Decisions on providing take-away doses need to strike a balance between risk management and patient autonomy, taking into consideration the risks to others and the community in general. When used appropriately, take-away doses can reinforce therapeutic engagement with easing the risks to the patient, their family and the community. For take-away dosing, prescribers should regularly (a minimum of every three months) assess the ongoing suitability of patients for take-away doses and document the assessment in the patient's records.

Note: Take-away dosing should be supported by appropriate documentation to protect the prescriber.

- When possible, efforts should be made to find an alternative to just providing doses to the patient, for example, encouraging the involvement of the family or guardian to play a role in collecting and handling take-away dosing for the patient. This should be done in consultation with managing team.

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

- Polysubstance use.
- Recent overdoses or presenting for dosing in an intoxicated state.
- Unstable psychiatric conditions.
- Risk of injecting take-home doses.

¹⁰⁰ State of Victoria, Department of Health and Human Services. *Policy for maintenance pharmacotherapy for opioid dependence*. Melbourne, Australia. 2016.

4.22 Improving retention of patients on methadone or buprenorphine

At treatment initiation, explain to the patient the need for comprehensive screening and how the service operates, provide clear explanations of methadone or buprenorphine maintenance therapy, the assessment processes involved and eligibility criteria, and provide all relevant information for long-term maintenance therapy and treatment.

- Effective treatment induction processes can help patients sustain the motivation to enter and remain in treatment.
- Ensure appropriate and adequate methadone or buprenorphine doses are administered to client: under-dosing will lead to acute drug cravings and retention is less likely.
- Ensure that services providing MAT within the community are available and accessible, as well as located at sites that are not too distant to where those with opioid dependency reside.
- Drug dependency is not an illness that can be cured with pharmaceuticals alone. MAT sites require staff that not only provide quality services in dispensing treatment but also have good communication skills, show empathy and provide psychosocial support to clients as needed. Investing in staff development in a range of skills will enhance patient retention.
- Prescriber, dispenser and other allied health staff need to provide additional counselling and social support on a routine and regular basis to address a range of health, social and economic challenges commonly experienced by patients. When various challenges are not addressed, retention is more difficult.
- Ensure the therapeutic alliance between the prescriber and dispenser towards the patient is strong. A positive relationship will encourage ongoing motivation to continue in treatment. Patients need to feel that they are being understood by the prescriber and dispenser, who are not only knowledgeable and supportive but also display empathy.
- When possible, encourage some flexibility in terms of opening and closing times of MAT services to further improve client engagement with treatment. Inflexible operating times can discourage long-term patient retention.
- The greater the travel distance for treatment, the less likely the patient is to be retained. When possible, and based on service capacity, assisting with some low-cost transport will help improve treatment retention.
- Promoting job satisfaction among staff will improve staff retention at MAT treatment sites. High staff turnover can adversely affect patient retention and have adverse impacts on effective programming.
- All services should promote and provide access to effective patient involvement and user groups at all levels of the service to empower patient autonomy. This will also lead to improved treatment retention.^{101 102}

101 Gowing L., Ali R., Dunlop A., et al. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

102 Chan B, Gean E, Arkhipova-Jenkins I, et al. *Retention Strategies for Medications for Addiction Treatment in Adults with Opioid Use Disorder: A Rapid Evidence Review*. Agency for Healthcare Research and Quality. Rockville, United States. 2020.

4.23 Switching from methadone to buprenorphine

Some patients may not tolerate methadone due to prolonged vomiting or severe constipation and will therefore prefer buprenorphine. Some patients may also request to switch to buprenorphine after spending time on methadone. If the patient has been free from opioid use due to methadone therapy, the managing team should attempt to discourage the switch to buprenorphine. However, if the patient rejects the advice to remain on methadone, then buprenorphine can be considered, if it is available.

The prescriber should be aware of precipitated opioid withdrawals in the initial period of switching from methadone to buprenorphine. The dose of methadone should be reduced to the extent that the client does not experience withdrawals with the reduced dose. Switching should not be done at doses of higher than 20 mg/day of methadone. After the methadone dose has been reduced to 15–20 mg per day (or less if the client can tolerate it), further doses of methadone should be withheld and the treatment team should wait for some withdrawal signs to emerge. With methadone, it may take more than one day for withdrawals to emerge. When the patient experiences some withdrawal-related discomfort, buprenorphine can be initiated. The first dose of buprenorphine can be 4–6 mg per day, which can be continued for a few days before the dose can be increased. The patient should be closely monitored in the initial few weeks. If the patient is not comfortable with the 'new' medicine and wants to switch back to the previous medicine, this should be allowed.¹⁰³

4.24 Switching from buprenorphine to methadone

Some patients may not benefit from buprenorphine and may continue to inject or use opioids by other routes despite being prescribed adequate doses. If a patient experiences intolerable side effects with buprenorphine, which may result in stopping the medicine, a switch to methadone can be considered.

It is important to explain to the patient the difference between buprenorphine and methadone. Highlight the possible increased chance of opioid overdose and the longer time it will take to build a maintenance dose with methadone. Patients need to be informed that it will take some days to wean off from buprenorphine and build an adequate dose of methadone. The patient may experience withdrawals during this time and should try to remain abstinent during this period, or at least adopt safer ways to use opioids.

Commence methadone 24 hours after the last dose of buprenorphine: from buprenorphine, doses of 8 mg daily and above, commence with 30 mg of methadone daily. From buprenorphine doses of 4–8 mg daily, commence with 20–30 mg of methadone daily. With buprenorphine doses below 4 mg daily, commence with less than 20 mg of methadone daily.¹⁰⁴

¹⁰³ Rao R, Ambekar A, Agrawal A. *Methadone maintenance treatment under National AIDS Control Programme, Practice Guideline*. Delhi, India. 2017.

¹⁰⁴ WHO. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. Geneva, Switzerland. 2009.

The prescriber should observe for opioid overdose symptoms when moving from buprenorphine to methadone. It is possible to reduce the dose of buprenorphine to as minimum a dose as is sufficient for withdrawal control in a day. Switching is usually not advised at buprenorphine doses of more than 8 mg/day. When the buprenorphine dose of 8 mg/day or less is achieved, further dose should be withheld until the patient experiences some withdrawal symptoms. However, a patient's pupils should never be constricted. When the patient exhibits withdrawal symptoms/signs, the first dose of methadone can be administered. The dose of methadone should be 15-20 mg on the first day, and this level of dosage needs to be continued for the next two to three days. Further increase should be as described in the induction phase above.¹⁰⁵

4.25 Transfer to another MAT site

Patients may temporarily transfer to MAT dispensing locations in other towns for work, holiday or other reasons. The patient's suitability for transfer must be assessed before making arrangements for it. The requirements and contraindications for providing take-away doses apply to patients seeking transfer.

Patients may also require permanent transfer to another prescriber or MAT site. Proper communication between the transferring and receiving prescribers and MAT sites is vital in each case. Without such communication, there is a risk of confusion about when the last dose was administered at the transferring dispenser, and the possibility of dual dosing on the same day, which can result in methadone toxicity. The prescriber who makes arrangements for the transfer must ensure that clear, written instructions are provided to both MAT sites about the timing of the last dose at the transferring site and the first dose at the receiving site.

The receiving prescriber should be provided with details such as the patient's name, date of birth, unique identification (ID), methadone or buprenorphine dose, dates of doses, the patient's address at the new location (if known) and the reason for transfer.¹⁰⁶

4.25.1 Receiving transfers

A prescriber who accepts a transferred patient must obtain adequate information from the transferring prescriber to ensure safety of treatment and continuity of care, and to facilitate decisions on take-away doses. It may be necessary to contact the transferring prescriber and request for the appropriate documents. The documents should include:

- The patient's full name, date of birth, unique ID and addresses (both old and new).
- Current methadone or buprenorphine dose in milligrams.
- Date and strength of the last methadone or buprenorphine dose provided under the transferring prescriber's care (including the number of take-away doses provided, if relevant).

¹⁰⁵ Ibid.

¹⁰⁶ Department of Health, Ministry of Health, The Republic of the Union of Myanmar. *Guidelines on Methadone Therapy in Myanmar (3rd edition)*. 2019.

4.26 Termination phase of treatment

Patients should be encouraged to remain in treatment for as long as they benefit from the programme. Treatment offers patients relief from the need to obtain drugs and an opportunity to stabilize their lives and withdraw from drug-taking culture. **Evidence suggests that the benefits increase when the patient remains in treatment for more than 12 months minimum**, and most opioid-dependent individuals continue to benefit from methadone or buprenorphine maintenance for many years.¹⁰⁷

4.27 Voluntary withdrawal from methadone or buprenorphine

Methadone and buprenorphine are effective treatments for opioid dependence, yet patients may wish to cease treatment for a variety of reasons. Stopping treatment is important to many patients and this topic should be discussed by the prescriber with the patient at regular intervals (such as every six months). Premature withdrawal should be discouraged, and the patient warned of the high risk of relapse, particularly if there is a rapid reduction of the dose. **Complete cessation is recommended only when the patient is socially engaged with 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.

The decision to withdraw and the rate of withdrawal may be determined by consultations between the patient, the prescriber and others in the treatment team (including the dispenser and the counsellor). Patients usually benefit from psychosocial support, including counselling, at this time. Monitor the patient closely during withdrawal, and if they experience difficulties, cease the dose reduction until they stabilize. Patients should have access to increased supportive counselling throughout voluntary withdrawal and, when possible, should be linked to community-based services or non-governmental organizations (international and national) that can provide after-care programmes and services to assist in the transition process.

Withdrawal can recommence after a period of stabilization. The patient may benefit from intensive counselling during and after the withdrawal process. The general guidance is that a reduction of the daily dose by 1 mg per fortnight or 25 mg per year is usually achievable when all social factors are favourable. In general, successful completion of withdrawal from methadone maintenance treatment is more likely if undertaken over a longer period. **Methadone must not be stopped abruptly** as the patient will experience withdrawal symptoms that could result in relapse to non-medical opioid use.

Methadone should be reduced at the following rate:

Dose greater than 50 mg	maximum of 5 mg/week.
Dose of 30-50 mg	maximum of 2.5 mg/week
Dose less than 30 mg	maximum of 1-2 mg/week

107 National Institute on Drug Abuse. 2018. *Principles of Drug Addiction Treatment: A Research-Based Guide* (Third Edition). NIDA, United States (Revised January 2018).

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.¹⁰⁸

Some patients may wish to be admitted into inpatient drug treatment facilities during the concluding phase of the tapering doses. If this situation arises, the patient and prescriber should discuss options and inpatient admission should be decided upon on a case-by-case basis.¹⁰⁹ However, the majority of patients undergoing methadone cessation do so as outpatients when they undergo a gradual tapering of the medication over several months. This approach provides the patients sufficient time to adjust to the necessary physiological, behavioural and social changes that they may experience during the cessation process. It is not uncommon for the severity of withdrawal to increase as the dose approaches zero, with peak withdrawal discomfort usually taking place one to four weeks after cessation of dosing. A low severity of various symptoms (poor sleep, mood disturbances, cravings) can often persist for several months and the patient needs to be informed and supported during this process to assist them from relapsing and using illicit or licit drugs to manage the symptoms.¹¹⁰

Patients withdrawing from **buprenorphine treatment** will generally tolerate greater incremental reductions than is the case with methadone. Buprenorphine dose reductions of up to 25 per cent every one to four weeks can be tolerated, provided patient stability is maintained.

Buprenorphine should be reduced at the following rates:

Dose greater than 8 mg	4 mg/week
Dose less than 8 mg	2-4 mg/week
Dose less than 2 mg	0.5-1 mg/week

The smallest dose available of buprenorphine-naloxone film is 2 mg; it has been reported that many patients find it difficult to cease from this level. Options at this dose include:

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

Whichever strategy is used, as with methadone, it is important to monitor the comfort and stability of the patient.^{111 112}

108 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

109 Department of Health, Ministry of Health, The Republic of the Union of Myanmar. *Guidelines on Methadone Therapy in Myanmar (3rd edition)*. 2019.

110 Ibid.

111 Gowing L., Ali R., Dunlop A., et al. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

112 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

4.28 Involuntary cessation of methadone and buprenorphine

It is possible to discontinue a patient's methadone or buprenorphine treatment if the patient is making unsatisfactory progress or putting themselves or others at risk. However, discontinuation of the treatment should be the last resort. The potential risks to the individual from cessation of methadone or buprenorphine 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 if available.

Reasons for involuntary cessation may include:

- Violent threats to or abuse of 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 treatment.
- Diversion of methadone.
- Trafficking of take-away doses.^{113 114}

An abrupt termination of treatment or a dramatic reduction in dosage is associated with a marked deterioration in behaviour, drug use and emotional stability, and is rarely warranted. Patients being discharged from the programme must be warned about the risks of opioid drug use, of possible reduced tolerance to heroin and subsequent risk of drug overdose. Patients should be informed of other treatment options. The prescriber should clearly document the reason/s for involuntary cessation of methadone or buprenorphine in the patient's clinical record. Even with involuntary cessation of methadone or buprenorphine, a plan to taper down the dose, similar to that outlined in the voluntary cessation of methadone or buprenorphine, should be implemented.¹¹⁵

4.29 Issues affecting treatment

4.29.1 Intoxication

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

- Moderately intoxicated patients should be asked to return later in the day, when they are no longer intoxicated (no longer experiencing constriction of pupils, itching/scratching or sedation), or asked to wait at the MAT site or treatment centre until they are alert.

113 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

114 Gowing L., Ali R., Dunlop A., et al. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

115 Queensland Health. *Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines*. Brisbane, Australia. 2018.

- Mildly intoxicated patients (less severe signs and symptoms than outlined above) should be assessed prior to the administration of a dose, and given a reduced dose (e.g., 50 per cent of the patient's normal methadone dose).¹¹⁶

4.29.2 Overdose

The risk of overdose is highest in the first two weeks of treatment, specifically with methadone. Overdoses are usually associated with the use of other sedatives, particularly benzodiazepines. Patients on buprenorphine are generally not at risk for overdose, except for individuals who use large amounts of benzodiazepines and are not tolerant to the effects of these sedatives. After stabilization of the methadone dose, those on higher doses are at a lower risk of overdose than those on lower (<60 mg) doses. This is thought to be due to the fact that high-dose methadone increases the individual's tolerance to opioids.

The treatment of overdoses in individuals on opioids, including methadone, consists of cardiopulmonary resuscitation (CPR), combined with initial drug therapy in the form of naloxone and monitoring in a hospital. Naloxone can be administered by intravenous, intramuscular, subcutaneous and intranasal routes. If the person overdosing does not respond within two to three minutes after administering a dose of naloxone, administer a second dose of naloxone. There is no limit to the quantity of naloxone that may be provided.¹¹⁷ Failure to rouse the patient following the administration of naloxone indicates an overdose from another sedative. As respiratory support with oxygen and ventilation are needed, the patient must be transported to a hospital.

The signs of an opioid overdose are:

Pinpoint pupils.
Peripheral cyanosis (blue tinge on the fingers).
Respiratory depression (not breathing).
Unconsciousness (or not react to loud noises).
Gurgling, snoring or choking sounds.
Have a slow or very faint pulse.

Naloxone should be stocked as an emergency medicine to combat opioid overdoses in general hospitals, drug treatment centres and, if available, drop-in-centres (DICs).

4.29.3 Missed doses

It is not uncommon for patients to miss supervised doses of methadone or buprenorphine. The reasons may be valid (family or employment commitments or transportation difficulties) or be related to continued drug use. It is often difficult to confirm why doses have been missed. If a patient misses doses intermittently (one to two a month), it does

116 Gowing L., Ali R., Dunlop A., et al. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

117 Jauncey ME., Nielsen S. Community use of naloxone for opioid overdose. *Aust Prescr*; 40:137-40. <https://doi.org/10.18773/austpr.2017>.

not necessarily indicate instability. Patients who regularly miss one or more doses a week should be reviewed by the managing team. If patients are missing doses due to non-medical use of opioids, the dose of methadone or buprenorphine should be increased.

In these circumstances, dispensers are advised to notify the prescriber, who should consider:

- The reasons for failure to attend the hospital/centre.
- The patient's use of drugs during this period.
- The patient's complaints of opiate withdrawal.
- Physical evidence of withdrawal or intoxication.

Table 4: Management of missed doses during MAT¹¹⁸

Number of days missed	Recommended action
1 day	Continue current dose, review at next appointment.
2 days	Review by managing team. Issues to be examined include: circumstances around the missed doses, including reasons for non-attendance; recent substance use and clinical presentation at dosing (including evidence of intoxication or withdrawal); and any relevant medical, psychiatric or social issues. Continue at current dose.
3 days	Review by managing team (assess as above). Give half methadone dose and resume normal dosing the following day. Continue current buprenorphine dose.
4 days	Review by managing team (assess as above). Give half methadone dose and resume normal dosing the next day. However, patient should be monitored closely by a clinician on subsequent days prior to dosing, aiming to return to the regular dose within 5 to 7 days. Give half buprenorphine dose and resume normal dosing the following day. Keep patient under close observation for the next few days.
5 days	Begin new induction.

118 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

4.29.4 Administration of incorrect doses

When a patient is seen by a new, inexperienced dispenser who is unfamiliar with the patient, errors can occur. It is not uncommon for new dispensers to confuse the methadone dose, mistaking milligrams for millilitres. This can result in the administration of very high doses. Once detected, patients should be observed for signs of sedation for four hours after the incorrect dose has been administered. If signs of intoxication continue, sending the patient to a hospital may be required. It is not recommended to induce vomiting; this may be dangerous and is contraindicated for patient with signs of CNS depression.

Incorrect buprenorphine dose administration does not generally require monitoring, except in the context of polysubstance use with other sedatives such as benzodiazepines. Under these circumstances, patients should be monitored for four hours after the incorrect dose for signs of intoxication or respiratory depression. The patient should be reviewed by the prescriber prior to the next dose of buprenorphine. It may be that a lower dose, or no dose, is required the following day (in effect, a two-day dose was administered).^{119 120}

4.29.5 Vomited doses

A vomited dose is only a concern with methadone, as buprenorphine is sublingually administered. Methadone is absorbed rapidly, so vomiting more than 20 minutes after administration of a dose will not result in much loss of the dose.

Table 5: Management of vomited doses during MAT¹²¹

Time of vomiting	Witnessed or unwitnessed	Action
Vomiting more than 20 minutes after dose	Witnessed or unwitnessed vomiting	Methadone has probably been absorbed, so no action required.
Vomiting less than 20 minutes after dose	Witnessed vomiting of methadone dose	Re-administer same dose of methadone.
	Unwitnessed vomiting of methadone dose	Review patient in four hours to assess whether or not the patient is experiencing withdrawal symptoms.
		Signs of withdrawal: give normal dose. No signs of withdrawal: do not administer an additional dose; resume normal dosage the following day.

¹¹⁹ Ibid.

¹²⁰ Gowing L., Ali R., Dunlop A., et al. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

¹²¹ WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

Patients sensitive to the emetic effects of opioids may require anti-emetic treatment (for example, pre-dose domperidone, prochlorperazine and metoclopramide) for a few days in the initial phase of treatment. Additional care is warranted in the case of pregnant patients because opioid withdrawal can cause foetal distress.

4.29.6 Combined drug toxicity

Overdose deaths due to methadone or buprenorphine alone are rare; they almost always involve other CNS depressant drugs, particularly psychoactive prescription drugs such as benzodiazepines or alcohol. The benzodiazepines flunitrazepam, clonazepam and diazepam are commonly identified in methadone-related drug deaths. Some methadone-related deaths occur due to the misuse of methadone tablets prescribed for pain, or the non-medical use of methadone following diversion from legitimately prescribed doses. Buprenorphine can produce respiratory depression but usually only in the presence of other sedating agents, particularly benzodiazepines.

Countermeasures:

- Warn the patient of the considerable risks of misusing psychoactive drugs (such as the benzodiazepines) and alcohol while on methadone.
- The programme should conduct random urine tests on clients during methadone treatment and the use of drugs should be discussed with the patient. Inform them about the risks of using alcohol and CNS depressant prescription drugs while on methadone treatment.

4.29.7 How to recognize a coma involving methadone or buprenorphine

Deaths from combined drug toxicity involving methadone or buprenorphine may be preceded by a long period of coma, during which the patient is left to "sleep it off" and subsequently dies. A methadone or buprenorphine patient who cannot be roused and makes noises suggestive of a blocked upper airway and depressed reflexes (snoring, gurgling or spluttering) has a very high risk of dying from a drug overdose.

Countermeasures:

- Inform the patient, family, friends and associates about the signs of coma and the urgency of acting if one is suspected. They should understand that it is a medical emergency if the patient cannot be roused and is snoring (or making other sounds that suggest airway obstruction).
- Comatose patients should be positioned on their side with their head extended (in a left lateral position) and taken to hospital immediately.
- A methadone-induced coma may require prolonged respiratory support and/or repeated administration of the opioid antagonist naloxone, often in an intravenous infusion over 24–36 hours. This can best be provided in an intensive care or high-dependency inpatient setting.
- Treatment of an overdose of buprenorphine is difficult as naloxone is ineffective at reversing it. For this reason, patients should be treated in hospitals. Treatment is restricted to supportive ventilation and correction of other underlying causes.

4.29.8 Other deaths associated with methadone maintenance

Risk-taking behaviour exposes many methadone patients to a high risk of death from injury, particularly due to road trauma, and homicide. Lifestyle factors such as poor nutrition and the high prevalence of smoking increase the risk of death from chronic non-communicable diseases, such as ischaemic heart disease and stroke. The non-medical use of injecting drugs is also associated with many infectious complications, such as sub-acute bacterial endocarditis, septicaemia and blood-borne viruses (HIV and hepatitis B and C). In some countries, suicide is the second most common cause of death among methadone patients (following drug overdose).¹²² Some methadone patients have a history of psychiatric illness, such as depression or psychosis, which may predispose them to the risk of suicide. They may have suppressed harmful emotions and symptoms during the period when they were injecting drugs, and these may become evident once they are stabilized with methadone maintenance therapy.

Countermeasures:

- Initial assessment of the patient should include a psychiatric evaluation.
- Look for signs of suicidal intent, depression and other psychiatric complaints throughout treatment.
- Refer co-occurring disorder patients (patients with dependence and a psychiatric illness) to a specialist methadone service for assessment and management, if appropriate.¹²³

4.29.9 Addressing constipation

Constipation can be one of the side effects of methadone and buprenorphine. A patient complaining of constipation after methadone or buprenorphine should be evaluated to rule out other causes of constipation. If an obvious cause is detected, appropriate treatment should be provided either by the MAT prescriber or through referral. If no other cause is identified, conservative measures should be initiated, such as dietary change, increased consumption of water, increased physical activity, etc. If these measures do not improve constipation, the client may be prescribed laxatives. If none of these measures alleviate the condition, the prescriber may need to consider decreasing the dose of methadone or buprenorphine, but this comes with an increased risk of withdrawal or relapse.

4.29.10 Addressing sleep disturbance

Sleep disturbances are common among MAT patients and include difficulty falling asleep or waking up multiple times throughout the night. A patient may have been using sedatives/benzodiazepine along with opioids prior to MAT. During treatment while the opioid-related withdrawals are taken care of by administration of methadone or buprenorphine, withdrawals related to sedatives are not addressed, which leads

122 Darke, Shane & Ross, Joanne. *The relationship between suicide and heroin overdose among methadone maintenance patients in Sydney, Australia*. *Addiction*. 96. 1443-1453. 10.1046/j.1360-0443.2001.961014438.x. 2001.

123 Department of Health, Ministry of Health, Union of Myanmar and WHO Myanmar Country Office. *Methadone Therapy in Myanmar for Prescribers and Dispensers*. 2004.

to sleep disturbance. If the patient is dependent on benzodiazepines, management of benzodiazepine dependence must be undertaken independent of MAT. For sleep disturbance, the patient may need to be educated on sleep hygiene patterns: establishing a fixed time to go to bed and avoiding afternoon naps and stimulating activities before bed, etc. If benzodiazepine medications are prescribed to assist with sleep, the dose must be kept low and should be prescribed for the shortest duration possible.

4.29.11 Addressing cardiac function

Prolongation of the QTc interval is a potential issue in patients treated with methadone and, less commonly, buprenorphine. The QTc interval is the measure of time between the onset of ventricular depolarization and completion of ventricular repolarization. A delay in ventricular repolarization (identified as a prolonged QTc interval, in which the heart muscle takes longer than normal to recharge between beats) can provoke arrhythmias, such as ventricular fibrillation and torsades de pointes, associated with sudden cardiac death. A QTc interval that is between 450 and 500 ms in men or 470 and 500 ms in women is considered mildly elevated, while anything over 500 ms is severe prolongation. QTc interval prolongation is evident in 10–15 per cent of people on methadone maintenance. The QTc interval normally varies depending on heart rate, age and sex. The QTc interval may be influenced by electrolyte balance, medications and ischaemia.

Assessment prior to initiating methadone

Routine electrocardiography (ECG) screening of patients seeking to commence methadone is *not recommended*. However, indications for ECG assessment prior to commencing methadone can be recommended for a patient with the following:

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

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

Responding to QTc prolongation during treatment

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

- Discuss implications of prolonged QTc interval with patient. Examine relevant clinical and family history.
- Continue methadone. But more frequent monitoring and recommend reduction of other risk factors (use of other drugs that may contribute prolongation of the QTc interval).
- If QTc interval remains prolonged, consider referral to drug dependency specialist or cardiologist. Trial of methadone dose reduction or transfer to buprenorphine.

For patients with severe prolongation of the QTc interval (>500 ms) or where there are clinical manifestations of QTc prolongation, the following options require consideration:

- Seek advice of drug dependency specialist and cardiologist (possible intensive investigation).
- Risk minimization strategy: reduce methadone dose, use of alternative MAT (buprenorphine) or discontinue methadone.
- Revisit the patient's methadone treatment plan, taking into consideration the likely impact of significant treatment changes on broader substance use and the patient's general health and welfare.^{124 125 126}

124 Gowing L., Ali R., Dunlop A., et al. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

125 Gheshlaghi F, Izadi-Mood N, Mardan A, et al. *Dose-Dependent Effects of Methadone on QT Interval in Patients under Methadone Maintenance Treatment*. ASIA PACIFIC JOURNAL of MEDICAL TOXICOLOGY. 2;1. 2013.

126 Alinejad, S., Kazemi, T., Zamani, N., et al. *A systematic review of the cardiotoxicity of methadone*. EXCLI Journal, 14, 577–600. 2015.

Chapter 5

Complementary treatments for those receiving Methadone or Buprenorphine



5. Psychosocial interventions

Psychosocial interventions are most effective when used in combination with methadone or buprenorphine. Retention in treatment is the most important factor in achieving effective outcomes of psychosocial interventions. Patients are more likely to participate in and continue with psychosocial interventions if they enjoy them. For this reason, they should be encouraged to engage in a number of psychosocial treatments over time in order to discover those that are best suited to their needs.¹²⁷

5.1 Contingency management

Contingency management is a method used to discourage problematic behaviour by rewarding desirable behaviour. In some techniques, undesirable behaviour leads to negative consequences. In essence, contingency management is a structured system of boundaries agreed upon by patients and their managing team prior to the initiation of treatment. It can be administered by any staff member with relatively little training. The major elements of contingency management are as follows:

- Clear definitions of desirable behaviours, 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 or conducting regular urine tests.
- Specified rewards, such as money, vouchers and take-home methadone or buprenorphine doses for desired behaviour.
- Positive personal feedback from the staff when desired behaviour is exhibited.

Contingency management can be related to any desirable behaviour that has specific outcomes with a potential for reward.^{128 129}

5.2 Cognitive-behavioural therapy (CBT)

Cognitive-behavioural therapy (CBT) should be administered by trained staff. In the case of opioid dependence, CBT has been used in various settings with positive outcomes. CBT focuses on the notion that behaviours are a function of beliefs. For example, substance

¹²⁷ Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. *A meta-analytic review of psychosocial interventions for substance use disorders*. Am J Psychiatry. 165(2):179-87. February, 2008.

¹²⁸ WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

¹²⁹ Stitzer M, Petry N. *Contingency Management for Treatment of Substance Abuse*. Annual Review of Clinical Psychology. 2:1, 411-434.

dependence is a learned behaviour capable of being modified through the correction of 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 on drug use, they will make better decisions on the use of drugs, resulting in reduced levels of use and harm. An example is being able to identify, and hence avoid, high-risk situations that might lead to relapse. The “behavioural” component of CBT aims to reinforce positive behaviour associated with good outcomes.^{130 131 132}

5.3 Brief motivational interviewing

Motivational interviewing (MI) is used to treat tobacco, alcohol and other substances. The key components of MI include establishing a “therapeutic alliance”, showing empathy, providing feedback and helping the client to reframe their behaviour to reinforce change. MI is a client-centred style of interaction that directs people to explore and resolve their ambivalence about their substance use (the ‘good things’ versus the ‘less good things’) and move through the various stages of change. It is useful when working with clients.¹³³

5.4 Peer-led programmes

People are well accepted by their peers within the drug-using community. Peer programmes, including peer education and peer group work, are an evidence-based intervention, and have been shown to be helpful in various cultural settings in building strong relationships with opioid-dependent individuals. Peer programmes are based on the concept that individuals who have good interpersonal skills and are interested in health-related learning can be trained to provide information and education to their drug-using community.

The role of a peer educator is to:

- Develop relationships with people who use drugs (PWUD) in the community.
- Provide information on health issues to PWUD in the community.
- Provide information on interventions to protect health and reduce risky behaviours.
- Provide referrals and link PWUD to local health services.

Peer educators should:

- Provide accurate, unbiased information to PWUD.
- Provide PWUD with information in a respectful manner.

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- 130 McHugh RK, Hearon BA, Otto MW. *Cognitive behavioral therapy for substance use disorders*. Psychiatr Clin North Am. 2010;33(3):511-525. 2006.
- 131 Pan S, Jiang H, Du J, Chen H, Li Z, Ling W, et al. *Efficacy of Cognitive Behavioral Therapy on Opiate Use and Retention in Methadone Maintenance Treatment in China: A Randomised Trial*. PLoS ONE 10(6). 2015.
- 132 Amini-Lari M, Alammehrjerdi Z, Ameli F, Joulaei H, Daneshmand R, et al. *Cognitive-Behavioral Therapy for Opiate Users in Methadone Treatment: A Multicenter Randomized Controlled Trial, Iran*. J Psychiatry Behav Sci. 11(2). 2017.
- 133 WHO. *The ASSIST-linked brief intervention for hazardous and harmful substance use: manual for use in primary care*. Geneva, Switzerland. 2010.

- Provide information that will help PWUD maintain their health.
- Maintain confidentiality, limit information to team members engaged in treatment.

Peer educator limitations:

- Peer educators are not nurses or doctors and cannot be expected to know everything.
- 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.^{134 135}

134 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

135 Stengel, C.M., Mane, F., Guise, A. et al. "They accept me, because I was one of them": formative qualitative research supporting the feasibility of peer-led outreach for people who use drugs in Dakar, Senegal. *Harm Reduct J* 15, 9. 2018.

Chapter 6

Populations with infections: HIV, HBV, HCV and TB



6. Patients with HIV

Sharing of injecting equipment is a common mode of HIV transmission among PWID. All PWID should be able, and encouraged, to access sterile injecting equipment to minimize their risk of becoming HIV infected. HIV-positive individuals should be counselled on the importance of using their own injecting equipment and ensuring its safe disposal. When a service provider is presented with PWID with HIV and opioid dependence, it is simpler to delay antiretroviral treatment (ART) until the patient is stabilized on MAT than to attempt to start ART before MAT.

6.1 Offering HIV testing and counselling to persons with opioid dependence

All persons with opioid dependence, including all PWUD (injecting and non-injecting), and their partners should be informed about the benefits of knowing their HIV status and the availability of effective treatment if they are diagnosed with HIV, and advised that the health condition is manageable with medication. All PWUD and their partners should be informed of the places where they can receive HIV Testing Services (HTS). This information can be distributed through medical facilities, rehabilitation centres, as well as through peer education and outreach programmes targeted towards PWUD. At all times, PWUD should be informed of their right to confidentiality and consent, and their right to refuse HIV testing if they choose. HTS may be provided in various settings, including mobile units or temporary testing sites, at drop-in centres, sites offering needle and syringe programmes, MAT sites, and health facilities dedicated to offering this service. The location and timing of HTS should be responsive to the needs and requests of all PWUD to maximize usage of such services. As an additional HTS option, Nigeria also offers HIV self-testing kits through various service delivery channels.

It is possible that HTS may be performed by trained peer outreach workers or lay providers, such as a trusted member of the drug-using community member, as has been recommended by WHO since 2016.¹³⁶ Patients with a positive-HIV status should be given priority access to methadone treatment, when appropriate. If illness or behavioural problems complicate the management of the patient, they may be referred to a specialist drug treatment centre or hospital infectious disease unit.

¹³⁶ World Health Organization, *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations*. Updated, 2016.

All people diagnosed with HIV should also receive counselling about how to avoid HIV transmission, including being provided with condoms and referrals by MAT staff to sites where needles and syringes are available. They should also be counselled about the benefits of testing for their partners and family members and offered support in notifying partners.

6.2 Opioid-dependent persons receiving antiretroviral therapy and wishing to start MAT

In 2018, an estimated 58 million people used opioids, and an estimated 11.2 million people injected drugs. The practice of injecting drugs accounts for roughly 10 per cent of HIV infections worldwide: it is estimated that more than 1 million PWID are living with HIV.¹³⁷ Studies have found that in many countries, particularly low- and middle-income nations, PWID who live with HIV are less likely to be accessing antiretroviral therapy (ART) than those not using drugs.¹³⁸ For all PWUD who are also living with HIV, access and adherence to ART is a prerequisite to ensure the virologic success in all patients. Supporting all PWUD (injecting or otherwise) to adhere to their treatment is an essential part of ensuring treatment is successful. However, studies have shown that PWUD can experience challenges to adhere to ART when they are considered less worthy to receive treatment due to widespread stigmatization and discrimination, including by health-service providers.¹³⁹ For PWUD already receiving ART and wishing to start on MAT, this should be strongly encouraged as studies show that it positively affects treatment adherence.¹⁴⁰

6.3 Rapid initiation of antiretroviral therapy for all people living with HIV

Rapid ART initiation should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment (strong recommendation: high-certainty evidence for adults and adolescents; low-certainty evidence for children). Rapid initiation is defined as within seven days of the HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation. ART initiation should be offered on the same day to people who are ready to start (strong recommendation: high-certainty evidence for adults and adolescents; low certainty evidence for children). WHO recommends that ART be provided at MAT sites.¹⁴¹

¹³⁷ UNODC. *World Drug Report 2021*.

¹³⁸ Harm Reduction International. *Global State of Harm Reduction*. London, UK. 2016.

¹³⁹ Iacob SA, Iacob DG, Jugulete G. *Improving the Adherence to Antiretroviral Therapy, a Difficult but Essential Task for a Successful HIV Treatment-Clinical Points of View and Practical Considerations*. Front Pharmacol. 2017;8:831. doi:10.3389/fphar.2017.00831. November, 2017.

¹⁴⁰ Andrea J. Low, Gitau Mburu, Nicky J. Welton, et al. *Impact of Opioid Substitution Therapy on Antiretroviral Therapy Outcomes: A Systematic Review and Meta-Analysis*. Clinical Infectious Diseases. Volume 63, Issue 8, 15. Pages 1094–1104. October, 2016.

¹⁴¹ WHO. *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach*. Geneva, Switzerland. 2021.

6.4 Referral of patient for antiretroviral therapy

PWID, as well as non-drug injectors, who are found to be HIV positive should be offered immediate referral for long-term care and treatment, preferably at a clinic or hospital whose staff have been sensitized and are respectful of PWUD. Community-based case management or peer navigation – with the use of peer educators and outreach workers – could facilitate treatment initiation and adherence support for PWUD. Commonly, PWUD will be fearful or and reluctant to approach medical services that have a historical record of not welcoming PWUD, particularly if stigma and discriminatory attitudes and practices towards them is prevalent. Facilitating connectivity of PWUD to the medical service offering ART is critically important in ensuring initiation of treatment and adherence. WHO guidelines recommend starting ART for all people with HIV, regardless of WHO clinical stage and at any CD4 cell count, including drug users with HIV.¹⁴²

6.5 Adherence support

For people dependent on opioids and living with HIV, MAT is an enabling factor for ART adherence. A case management approach is an effective model for maintaining long-term compliance for ART when receiving services at a health-care facility. It is recommended to invite the client to prevention and treatment literacy sessions, to ensure that they fully understand the purpose of medical procedures and future steps associated with ART. Some strategies recommended for effective ART adherence support are as follows:

- Provide adherence support for the first six months of ART.
- Encourage a collaborative team approach that involves community-based services with a peer educator/outreach worker and the support of MAT sites. The focus is to discuss and explore risk assessment, offer adherence support during the intensive case management phase, identify “dropouts” from ART, and seek solutions to encourage adherence.
- Many PWUD may have fears and concerns about ART. These should be addressed by providing appropriate and factual information in a way that can be easily understood. The patient needs to be counselled about the benefits of initiating ART before feeling unwell or displaying symptoms. Clearly explain that adherence to ART will suppress viral load, which will support and promote good health and minimize complications with treatment. A topic of discussion should be the use of condoms to prevent transmission of HIV to sex partners.
- If a patient ceases ART, a detailed assessment of the reasons that led to treatment termination should be examined.
- Services involved in providing ART to a patient should have mechanisms in place for continuity of treatment for those placed in detention or prison, including post release.¹⁴³

¹⁴² WHO. *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations*. Updated, 2016.

¹⁴³ UNODC et al. *Implementing comprehensive HIV and HCV programmes with people who inject drugs: practical guidance for collaborative interventions*. Vienna, Austria. 2017.

6.6 Counselling patients regarding interactions between methadone, buprenorphine and antiretroviral (ARV) medications

Methadone interacts with a number of ARV medications and may reduce the effectiveness of some of them, while increasing the side effects of others. Similarly, ARV medications can alter the level of methadone in the blood, so careful monitoring of symptoms is required during the commencement of ART in patients on methadone. Dose adjustments may be necessary. Interactions between buprenorphine and ARV 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 between ARV medications and methadone is found in **Appendix 3**.

6.7 Hepatitis B and C virus (HBV and HCV)

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are major causes of acute and chronic liver disease, and disproportionately affect PWID worldwide. Health-service providers, including those at MAT sites, working with PWID should improve their knowledge and capacity to prevent, diagnose and educate PWID about these conditions, and should be well versed on treatment regimens to adequately support PWID with HBV and HCV. Treatment of HBV and HCV is as effective in people with a history of opioid dependence who are currently engaged in MAT as in other population groups. PWID should be vaccinated against HBV and OST sites could facilitate this process on-site or arrange referral to appropriate health centres. Testing for HCV should be offered to all PWID, and in case of presence of chronic HCV infection, further linkage to care and treatment with direct acting antivirals (DAA) should be provided. Integration of HCV testing and treatment services into OAMT sites may be considered where possible, as this will improve access to HCV care and result in better treatment outcomes.^{144 145} Testing must be non-coercive and voluntary, and the implications of the testing process must be clearly understood by the patient. International guidelines are available for testing and treatment of HBV and HCV, including for PWID.^{146 147}

6.8 Tuberculosis and opioid dependence: Screening opioid-dependent persons for TB

TB is not uncommon among PWUD because of the low socioeconomic status and poor general health and nutrition of many opioid-dependent patients. Many PWUD are also HIV-positive, which further compromises their nutritional and health status. Opioid-dependent persons identified to be HIV infected should be assisted by service providers to undergo routine and regular TB screening.

144 WHO. *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection*. Geneva, Switzerland. 2018.

145 WHO. *Access to hepatitis C testing and treatment for people who inject drugs and people in prisons – a global perspective*. Policy brief. Geneva, Switzerland. 2019.

146 WHO. *Guidance on prevention of viral hepatitis B and C among people who inject drugs*. Geneva, Switzerland. 2012.

147 WHO. *Guidelines on hepatitis B and C testing*. Geneva, Switzerland. 2017.

6.9 Stabilizing opioid-dependent persons on methadone or buprenorphine to improve adherence to anti-TB medication

Patients with opioid dependence may adhere better to the complex anti-tuberculosis treatment (ATT) regimen once their drug use has been stabilized with methadone or buprenorphine. This also helps to improve retention in treatment. Patients taking supervised or directly observed MAT and needing treatment for TB should be supported with both medicines.

6.10 Counselling patients on interactions between methadone or buprenorphine and anti-TB medication

Several medications used for the treatment of TB, in particular rifampicin, can interact with methadone. For a full discussion of these interactions see **Appendix 3**. To know more about the prevention, treatment and care of TB in people who inject drugs, refer to other guidance documents.¹⁴⁸

For referrals for TB therapy, integrating services between MAT and TB for better continuum of care, effective use of peer navigation techniques and ensuring adherence support when receiving treatment should mirror the approach used for those on MAT who are also living with HIV.

148 WHO. *Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs: Consolidated guidelines*. Geneva, Switzerland. 2016.

Chapter 7

Populations with special needs



7. Managing acute or chronic pain during methadone or buprenorphine therapy

It is important not to assume that a maintenance dose of MAT will manage all pain. Patients suffering from **acute pain** during methadone or buprenorphine therapy 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. It may be necessary to increase the MAT by 10-15 per cent for a limited time (one to two weeks) and to split the dose. The management of severe acute pain in patients who are on methadone or buprenorphine and require hospitalization should be similar to that of other patients (e.g., by using parenteral opioids), except that a higher dose of the treating opioid may often be required due to opioid tolerance. When possible, the methadone or buprenorphine dose should be continued during the hospital stay, with additional opioid analgesics, if necessary. Outpatients who have been stabilized on methadone or buprenorphine and experience acute severe pain may require opioid doses that are higher than normal to overcome tolerance. In some cases, they may also require a temporary increase in their methadone or buprenorphine dose. Discussion of such cases with an experienced drug treatment specialist should be considered.

People with **chronic pain** receiving methadone or buprenorphine should be treated as any other patient with non-opioid use. The origin of chronic pain should be clinically investigated prior to treatment with methadone or buprenorphine. Referral to a specialist is recommended, and a second opinion may be sought. Patients suffering from chronic pain often have significant psychosocial and mental health problems, which should be managed during treatment. Avoid the use of other psychoactive medications, as there is no evidence of effectiveness in pain relief (e.g., benzodiazepines, antidepressants).^{149 150}

7.1 Management of patients with sickle cell disease

Sickle cell disease (SCD) is an inherited disorder of hemoglobin structure that predominantly affects individuals of African descent and is the most common hemoglobinopathy. Millions of people are affected globally with SCD, and the condition is also commonly found in Nigeria. The hallmark of SCD is vaso-occlusive pain that may be acute and episodic or may progress to chronic and persistent pain. Management of sickle pain includes

149 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

150 Gowing L., Ali R., Dunlop A., et al. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

approaches that are pharmacological and nonpharmacological (e.g., hot baths and warm compresses). In many countries, patients with SCD rely on opioids almost exclusively for acute and chronic pain management. Currently, buprenorphine, in combination with naloxone, appears to be the best treatment for acute and chronic SCD pain.^{151 152} Management of acute or chronic pain among PWUD that also have a diagnosis of SCD is as discussed above.

7.2 Management of patients with co-existing mental health problems

PWID and those who are opioid-dependent commonly have psychiatric comorbidities that need to be managed. It is often difficult to tell whether there is a causal relationship between substance use and mental health problems. A number of different mental health conditions accompany opioid dependence. These include depression, social phobia and other anxiety disorders.¹⁵³ Such patients may need to be referred to a psychiatrist or a health professional with a mental health background.

7.3 Depression and anxiety in persons with opioid dependence

Depression is a common mental health problem and is more prevalent among people who use drugs; in fact, it is the most common co-occurring psychiatric disorder among PWUD. Anxiety is also a widespread problem and is often associated with substance use. Anxiety may be related to withdrawal symptoms and may subside with MAT. Depression can be more difficult to manage. Patients diagnosed with depression should be treated pharmacologically when possible. The pharmacological treatment of depression takes around two to six weeks to have an initial impact. The treatment should be continued for at least six months after the first episode of depression.

7.4 Depression and risk of suicide: Risk assessment and management

Recognizing depression and treating it effectively often results in positive outcomes. The clinical features of depression include feelings of sadness, crying, irritability, low self-esteem, guilt or pessimism, suicidal ideation, difficulty concentrating or forgetfulness, lack of interest in pleasurable activities, lack of energy, sleep disturbance, appetite disturbance and agitation.

The most serious aspect of depression is the risk of suicide. It is important to assess this risk in all patients presenting with depressive symptoms. People who use drugs, particularly those with comorbid depressive disorders, have a higher risk of suicide. It is important to:

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- 151 Ballas, S.K. *Opioids and Sickle Cell Disease: From Opium to the Opioid Epidemic*. J. Clin. Med. 10, 438. <https://doi.org/10.3390/jcm10030>. 2021.
 - 152 Sinha CB, Bakshi N, Ross D, Krishnamurti L. *Management of Chronic Pain in Adults Living With Sickle Cell Disease in the Era of the Opioid Epidemic: A Qualitative Study*. JAMA Netw Open. 2019;2(5): e194410. doi:10.1001/jamanetworkopen. 4410. 2019.
 - 153 Lingford-Hughes, A. R., Welch, S., Peters, L., & Nutt, D. J. *BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP*. Journal of Psychopharmacology, 26(7), 899-952. 2012.

- a. Assess suicide risk by examining the following:
 - What is the current degree of suicidal ideation?
 - Actively suicidal (any plans?)
 - Ambivalent about suicide?
 - Passively suicidal or no ideation?
- b. Assess for previous attempts at suicide (number of previous attempts and those that required medical intervention).
- c. Assess the person's psychiatric status and if the person is psychotic.
- d. Lastly, assess the person's social support network and review for any other risk factors, such as homelessness or unemployment.

Depressive patients who are suicidal may be helped by hospitalization and prescription antidepressants. It is extremely important to be vigilant and educate family members about the patient's suicidal behaviour.

7.4.1 Pharmacotherapy for major depressive disorder

Antidepressants are the first choice for moderate-to-severe depressive disorder. For those who experience additional psychotic symptoms, the use of antipsychotics may also be considered. Antidepressants for consideration may include tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).

7.5 Management of anxiety

Persistent anxiety is manifested as fear of unknown origin, a feeling of tremulousness, palpitation, racing of the heart and profuse sweating (evident during a handshake with an anxious person). The duration of anxiety may vary depending on the cause. The common causes of persistent anxiety among people who use drugs are alcohol withdrawal, benzodiazepine withdrawal and generalized anxiety disorder. The frequent causes of acute anxiety attacks are panic disorder, substance-induced panic episodes, hypoglycaemia and hyperventilation.

Features of generalized anxiety disorder include restlessness or nervousness, fatigue, difficulty concentrating, irritability, tension, trembling, sweating, palpitations, dizziness, sleep disturbance and abdominal discomfort.

Treatment:

- Relaxation techniques (e.g., Jacobson muscle relaxation technique).
- Supportive psychotherapy (reassurance, explanation, expert advice, suggestions, guidance, ventilation, support and facilitating emotional support from key people).
- Pharmacotherapy.

If treatment of anxiety with antidepressants is required in combination with methadone, non-sedating antidepressants (e.g., SSRIs) are preferred, considering interactions with methadone.

Benzodiazepines are prescribed only for a short period of time. It is better to avoid

their use in the treatment of generalized anxiety disorder, as they should not be used to alleviate symptoms caused by the minor stresses of everyday life. Driving should be avoided. Educating the patient is critical to the effective management of generalized anxiety disorder.

7.6 Psychotic episodes due to drug use

Primary psychotic disorders can be the result of drug use, head injury or acute infection. Amphetamine-type stimulants (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. Normally, medication is not required to resolve drug-induced psychosis. Patients who have psychosis and who do not have a recent history of the use of stimulants or hallucinogens may have a primary psychosis, such as schizophrenia. Primary psychoses are difficult to manage, and the patient should be referred to a mental health-specific service. Opioids (including methadone) will exacerbate the sedative effects of antipsychotics.^{154 155}

7.7 Opioid dependence, contraception and pregnancy

Research has found that women experiencing a substance use disorder seem less likely than other women to utilise the most effective forms of contraception. The primary contraceptive method used by women who use drugs is often condoms. However, condoms are only 'moderately effective' as they require the woman dependent on drugs to take decisive action at every sexual encounter. Implant and intrauterine devices that are generally considered more effective than condoms are less likely to be used by women taking substances.^{156 157} Studies have found that women receiving methadone treatment have lower rates of contraceptive use, higher rates of unintended pregnancy and generally more ambivalent attitudes toward pregnancy compared to the general population. Proactive planning is critical for women to realize their reproductive goals, and service providers should highlight that contraception, including hormonal options, is not contraindicated for women on methadone or buprenorphine.¹⁵⁸

Women who suffer from opioid dependence tend to be in their fertile years, which means that pregnancy is not uncommon among female patients. It is important to engage women

154 WHO Regional Office for South-East Asia. 2008. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India.

155 Gordon, A. *Comorbidity of mental disorders and substance use: A brief guide for the primary care clinician*. National Drug Strategy Monograph Series. 71. 2008.

156 Terplan, M., Hand, D. J., Hutchinson, M., Salisbury-Afshar, E., & Heil, S. H. *Contraceptive use and method choice among women with opioid and other substance use disorders: A systematic review*. Preventive Medicine. 80, 23-31. 2015.

157 Joanne Neale, Helena Werthern, Nour Alhusein, Angel Chater, Jenny Scott & Hannah Family. *Contraceptive choice and power amongst women receiving opioid replacement therapy: qualitative study*. Drugs: Education, Prevention and Policy. DOI: 10.1080/09687637.2021.1954599. 2021.

158 Curtis KM, Tepper NK, Jatlaoui TC, et al. *U.S. Medical Eligibility Criteria for Contraceptive Use, 2016*. MMWR Recomm Rep 2016;65(No. RR-3):1–104. DOI: 10.15585/mmwr.rr6503a1. 2016.

in the early stages of pregnancy and retain them in treatment to optimize antenatal care. Conduct screenings for other substance use and mental health issues, as well as for blood-borne viruses. Folate supplementation and psychosocial support should also be provided. Opioid withdrawal is generally not recommended during pregnancy as it results in poorer pregnancy outcomes.¹⁵⁹

Methadone and buprenorphine can be an option for the management of opioid dependence during pregnancy and is safe and effective during pregnancy for both mother and neonate.^{160 161} As pregnancies in this population are not planned in most cases, advice on family planning and birth control, including effective contraception, needs to be offered to women seeking treatment for opioid dependence.

In general, methadone treatment for pregnant women should:

- Stabilize the patient on an appropriate dose that is sufficient to cease the use of illicit drugs.
- Maintain the patient at a level that is comfortable for her and that avoids drug withdrawal during pregnancy. Do not encourage a reduction of the dose.
- Reassess the dose in the days immediately following delivery to avoid over-sedation. Keep the patient on the maintenance dose for a minimum of two to three months postpartum before reducing the dose.
- Consider the need to address other substance abuse problems (smoking, alcohol, benzodiazepines) that have adverse effects on pregnancy outcomes.^{162 163}

For buprenorphine treatment during pregnancy, in some countries, buprenorphine-mono is preferred, rather than the combined buprenorphine-naloxone product. It is reported that with the buprenorphine-naloxone film, the absorption of naloxone is minimal when administered sublingually. However, the effect of long-term, low-level naloxone exposure on the foetus is unknown.¹⁶⁴

Research shows methadone to be associated with greater treatment satisfaction and retention for pregnant women, despite higher risk linked to drug interactions and adverse events. Buprenorphine has fewer drug interactions but comes with a precipitated withdrawal – the risk this may pose to the foetus should be taken into consideration, particularly during the induction and stabilization period.¹⁶⁵

159 WHO Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

160 Dunlop, A., Petroulias, D., Marope, D., Khoo, K., Kimber, J., Ritter, A., Osborn, D. A. *Pharmacotherapies and pregnancy*. In R. P. Mattick, R. Ali & N. Lintzeris (Eds.). *Pharmacotherapies for Opioid Dependence Treatment* (pp. 282-329). London, UK. Informa Healthcare. 2009.

161 WHO. *Guidelines for the identification and management of substance use and substance use disorders in pregnancy*. Geneva, Switzerland. 2014.

162 Department of Health, Ministry of Health, The Republic of the Union of Myanmar. *Guidelines on Methadone Therapy in Myanmar (3rd edition)*. 2019.

163 WHO. *Guidelines for the identification and management of substance use and substance use disorders in pregnancy*. Geneva, Switzerland. 2014.

164 Queensland Health. *Queensland Medication-Assisted Treatment of Opioid Dependence: Clinical Guidelines*. Brisbane, Australia. 2018.

165 Ibid.

MAT is thought to have minimal long-term developmental impacts on children when compared to the risk and resulting harms of uncontrolled opioid use during pregnancy.¹⁶⁶

7.7.1 Increasing methadone or buprenorphine doses during and after pregnancy

As pregnancy proceeds and fluid retention increases the volume of distribution, the dose of methadone may need to be increased. Due to other metabolic changes, the dose of methadone may have to be increased by 5 mg to 10 mg or, occasionally, by more in the latter half of pregnancy. The need for split-dosing (twice daily) may be required in some cases. The situation is assessed by considering whether the patient is experiencing withdrawal symptoms. The dose may need to be reduced postpartum. The dose will need to be reduced by 5 mg to 10 mg (depending on how much the dose was increased by). Breastfeeding while on methadone is not associated with adverse outcomes and should be recommended to all women.¹⁶⁷

For buprenorphine, dose increases may be required throughout pregnancy, especially during the second and third trimesters. A proportion of clients on buprenorphine will experience withdrawal symptoms when buprenorphine dosing occurs less frequently (e.g., double dosing), therefore it is recommended that patients are dosed daily during pregnancy.¹⁶⁸

7.8 Neonatal abstinence syndrome

Neonatal abstinence syndrome (NAS) is an opioid withdrawal syndrome commonly experienced by newborns following birth when the mother is opioid-dependent in general, and for those receiving MAT. However, studies have found that the incidence of NAS was significantly higher in infants whose mothers were exposed to methadone compared to buprenorphine.¹⁶⁹ Withdrawal generally commences within 48 hours of delivery, though it may be delayed in cases of polysubstance dependence, particularly those that involve other sedatives such as benzodiazepines (delays of up to 14 days have been reported in a small number of cases). Monitoring should continue for at least seven days in most situations.

Not all newborns suffer from NAS and although NAS is more likely to develop in the infants of mothers with a higher level of opioid dependence, this is not always the case. Severity of withdrawal is probably improved if neonates can be kept with their mothers, and when breastfeeding is encouraged. Indications for treatment of NAS include the

166 WHO, Department of Mental Health and Substance Abuse. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. Geneva, Switzerland. 2009.

167 WHO, Regional Office for South-East Asia. *Operational guidelines for the management of opioid dependence in the South-East Asia Region*. New Delhi, India. 2008.

168 Winklbaaur, B., Kopf, N., Ebner, N., Jung, E., Thau, K., and Fischer, G. *Treating pregnant women dependent of opioids is not the same as treating pregnancy and opioid dependence: A knowledge syntheses for better treatment for women and neonates*. *Addiction*. 103: p. 1429-1440. 2008.

169 Ravi Bhavsar, Alla Kushnir, Nicole Kemble. *Incidence and Severity of Neonatal Abstinence Syndrome in Infants with prenatal exposure to Methadone versus Buprenorphine*. *Pediatrics*; 142 (1_MeetingAbstract): 145. 10.1542/peds.142.1MA2.145. May, 2018.

following: seizure, weight loss (poor feeding, diarrhoea and vomiting, dehydration), poor sleep and fever. The Modified Finnegan Scale is the most comprehensive scale used to assess the presence and severity of NAS. Treatment should be based on the severity of the withdrawal signs and be commenced when a score of nine or more on the Finnegan Scale (see **Appendix 8**) is recorded on two consecutive observations. Improvement should be monitored using scores on the Finnegan Scale. Long-term follow-up (e.g., 12 to 24 months) may be required to monitor for developmental abnormalities.

7.9 Polydrug use and methadone or buprenorphine

Polydrug use is the simultaneous use of multiple psychoactive substances (legal or illegal) by an individual. Among many PWUD, polydrug use has various functions:

- It can maximize the effects of other drugs.
- It can balance or control the negative effects of other drugs.
- It can substitute sought-after effects of other drugs.
- It can prolong the pleasurable experiences of other drugs.

Use of alcohol, benzodiazepines, antidepressants or other sedatives (in doses outside the normal therapeutic range) in conjunction with opioids is of particular concern due to the increased risk of overdose, particularly during methadone or buprenorphine induction and during withdrawal. Polydrug use should be regularly assessed prior to and during treatment for opioid dependence. Referral to specialist services is recommended for those misusing or dependent on multiple drugs or alcohol. However, polydrug use should not be a reason to withhold MAT. Awareness of withdrawal and intoxication from commonly used drugs among MAT service providers can be useful during assessment and ongoing care of the patient.¹⁷⁰

Those on methadone or buprenorphine may also be using various additional drugs. It is useful for the prescriber and dispenser to be aware of various withdrawal symptoms and states of intoxication that can arise from commonly used drugs.

7.9.1 Alcohol

Harmful alcohol consumption is not uncommon among those on MAT. Prescribers and dispensers should be aware and detect hazardous alcohol consumption patterns and intervene to minimize adverse interactions with MAT. Alcohol consumption should be monitored by history, examination of the patient and awareness of signs and symptoms of alcohol intoxication. When appropriate and available, conducting liver function tests can be useful. Alcohol breathalyzer is an option but adds an additional cost and may not be available in all settings. Methadone or buprenorphine should not be administered to a patient who presents noticeably intoxicated with alcohol or any other drug. Requesting the patient to rest and wait for a further review at a later time or the following day is recommended to ensure their health.

170 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Polydrug use EMCDDA 2002 selected issue In EMCDDA 2002 Annual report on the state of the drugs problem in the European Union and Norway. 2002.

Patients who are using alcohol or other non-opioid drugs in a potentially harmful way at the time of their entry to MAT should be counselled on the dangers of intoxication. They should be informed of the harms of polydrug use and possible increased risk of overdose and advised on the ways to reduce or stop hazardous use of alcohol and other drugs when receiving MAT.^{171 172}

7.9.2 Benzodiazepines

Benzodiazepine users have commonly been found to exhibit general patterns of anxiety, increased risk and poorer psychological functioning than other patients. Benzodiazepine use and increased risk of overdose, as well as vulnerability to increased risk of road traffic accidents, highlight the need to address misuse of benzodiazepines, particularly when combined with opioid drugs, such as methadone. It is recommended that caution be observed when prescribing benzodiazepines to those on MAT. Methadone or buprenorphine treatment may trigger the onset or worsening of benzodiazepine misuse. Consequently, patients receiving maintenance benzodiazepines should receive close clinical supervision.^{173 174}

7.10 Treating polydrug use

Patients dependent on various drugs may prefer to withdraw from one drug at a time due to personal fear and anticipated discomfort of detoxification. Whether as inpatient treatment, residential rehabilitation or outpatient, patients should be encouraged to address all forms of problematic drug use simultaneously. A person attempting to abstain from one drug may relapse when using another drug. General counselling is often more effective when a patient's multiple drug problems are addressed simultaneously.

Focusing on one drug to the exclusion of others may result in limited improvement in the patient's overall functioning, despite a reduction in drug use. Difficulties and challenges will arise when treating polydrug use, but on the other hand there are advantages in terms of savings in time and costs, and simultaneous treatment leads to better health outcomes. However, having the patient's support and willingness to engage in this treatment approach will produce a better outcome.¹⁷⁵

171 Gowing L., Ali R., Dunlop A., et al. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

172 Nolan S. Klimas J, Wood E. Alcohol use in opioid agonist treatment. *Addict Sci Clin Pract* 11:17 DOI 10.1186/s13722-016-0065-6. 2016.

173 Jones, J. D., Mogali, S., & Comer, S. D. *Polydrug abuse: A review of opioid and benzodiazepine combination use*. *Drug and Alcohol Dependence*, 125(1-2), 8–18. 2012.

174 Chen K, Berger C, Forde D, et al. *Benzodiazepine Use and Misuse Among Patients in a Methadone Programme*. *BMC Psychiatry* 11:90. 2011.

175 Gowing L., Ali R., Dunlop A., et al. *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*. Canberra, Australia. 2014.

APPENDICES



Appendix 1

Glossary of terms

Agonist	A substance that binds to and activates a particular type of receptor. It produces effects similar to those of a substance.
Amphetamine-type stimulants	A group of drugs, mostly synthetic in origin, whose principal members include amphetamine, methamphetamine and MDMA (ecstasy). Use of these substances has a stimulatory effect on the central nervous system and influences the levels and action of the important neurotransmitters: dopamine, norepinephrine and serotonin. These substances have stimulant properties.
Analgesic	A substance that reduces pain and may or may not have psychoactive properties.
Antagonist	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 that it blocks and prevents activation of the opioid receptors.
Brief intervention	A treatment strategy in which structured therapy of a short duration (typically five to 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.
Buprenorphine	A partial opioid agonist used for the treatment of opioid dependence.
Clinical Opiate Withdrawal Scale	A clinician-administered written instrument that rates 11 common opiate withdrawal signs or symptoms.
Dependence	As a general term, the state of needing or depending on something or someone for support or to function or survive. It implies a need for repeated doses to feel good or to avoid feeling bad. The term "addiction" was more commonly used in the past but is now considered stigmatizing and has, to large extent, been replaced by the term "dependence".
Dependence syndrome	A cluster of behavioural, cognitive and physiological phenomena that may develop after repeated substance use. Typically, these phenomena include a strong desire to take a drug, impaired control over its use, persistent use despite harmful consequences, increased tolerance and a physical withdrawal reaction when substance use is discontinued.

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 per cent of an administered medication.
Human immunodeficiency virus (HIV)	The virus that causes HIV/AIDS, transmitted through blood, semen, vaginal fluid and breast milk. There are treatments available to prevent HIV from progressing to AIDS but there is currently 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.
Needle and syringe programme	A type of harm reduction initiative that provides clean needles and syringes to people who inject drugs to reduce transmission of HIV and other blood-borne viruses (such as hepatitis B and C).
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 can 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>) and their synthetic analogues and compounds. Synthesized in the body, these substances 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. Desired changes include raising awareness and modifying 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. Pharmacotherapy of opioid dependence is not limited to methadone maintenance therapy.
Polydrug 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 drug-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 PWUD relapse several times before they achieve long-term abstinence.
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 that 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.

Appendix 2

Risks of treatment with methadone or buprenorphine and countermeasures

Risks	Countermeasures
Complicated pharmacokinetics, prescriber/dispenser unfamiliarity.	Prescriber/dispenser training; a registration system.
Dosing by multiple prescribers and dispensers.	A standardized registration system for the patients is developed and practised.
Poor compliance and diversion to illicit use and trafficking.	A supervised dosing programme; monitoring and limiting of the number of take-away doses.
Trafficking and consequent overdosing of non-tolerant people not on the methadone programme.	Tight control of take-away doses; discretion in judging patient suitability for take-away doses.
Illicit injection of take-away doses.	Dilution of methadone take-away doses to at least 200 millilitres; discretion in judging patient suitability for take-away doses.
Accidental poisoning of children.	Take-home doses stored in childproof containers (locked away and kept out of reach from children. Should not be kept in a fridge or cabinet where foods are stored).
Client receives dose at one clinic and when transferred to another clinic receives an additional dose on the same day at the time of transfer.	Meticulous arrangements during the registration process at time of transfer.
A high risk of drug overdose in the first 10 days of methadone treatment.	Meticulous care and frequent patient review in the first 10 days of methadone dispensing; dispenser alertness to signs of toxicity.
Precipitated withdrawal can take place with buprenorphine if given too soon after other opioid use. Not dangerous but can be extremely uncomfortable. May result in the patient refusing treatment.	Patients counselled to not consume opioids within six hours of the first dose of buprenorphine. Continue with buprenorphine dosing and provide symptomatic medication as needed.

Risks	Countermeasures
A high risk of combined drug toxicity – risk higher with methadone.	Dispenser alertness to signs of toxicity: comprehensive assessment, understanding the management of polydrug abuse, warning to patient about risk, and education of family/friends about signs of overdose and coma (unroutable, snoring, respiratory depression, cyanosis).
Overdose risk increased with respiratory problems – risk higher with methadone.	Careful assessment, lower starting doses, smaller and slower dose increases, inpatient treatment, and appropriate medications for all respiratory problems such as asthma, bronchitis and tuberculosis.
Injury.	Warn patient about the risks of driving/using machinery before dose stabilisation and while the dose is being adjusted.
Psychiatric comorbidity, including suicide risk.	Assessment of suicide risk, assessment of patient psychiatric status, maintenance of a high index of suspicion, timely response to suicide risk, and referral to specialist MAT service if appropriate for management of dual disability.
Discontinuation of treatment.	Set up of supervised dosing to be as convenient as possible. Discrete use of take-away doses.

Appendix 3

Interactions between MAT and commonly used medications

Interactions between methadone or buprenorphine and commonly used medications for HIV, hepatitis B and C, and TB may occur as a result of an alteration in the metabolism of the MAT by the hepatic cytochrome p450 system. ART-MAT interactions may result in symptoms of withdrawal or over-sedation, requiring an adjustment in the dose. The effect of methadone (less so with 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.

Interaction between ARVs and methadone

ARV	Effect of ARV on methadone	Effect of methadone on ARV	Comments
Nucleoside reverse transcriptase inhibitors (NRTIs)			
Zidovudine (AZT)	Zidovudine had no effect on methadone pharmacokinetics.	Methadone increased zidovudine AUC (29–43 per cent).	Routine dose modification of zidovudine is not warranted with co-administration, but patients should be monitored closely for potential toxicity of zidovudine: anaemia, neutropenia, nausea, myalgia, vomiting and headache.
Lamivudine (3TC)	No effect of lamivudine on methadone pharmacokinetics observed.	None reported.	No known interactions; no dose adjustment necessary.
Emtricitabine (FTC)	Co-administration has not been studied, but based on data from lamivudine and tenofovir, a clinically relevant drug interaction is unlikely with FTC.	Not studied.	No known interactions.
Tenofovir disoproxil fumarate (TDF)	Co-administration of TDF had no clinically significant effect on the pharmacokinetics of methadone in subjects stable on methadone maintenance therapy and no pharmacodynamic effects were noted.	Not reported.	No dose adjustment necessary.
Abacavir (ABC)	Methadone clearance increased by 22 per cent. Patients should be monitored for methadone withdrawal symptoms; dose increase unlikely, but may be required in a small number of patients.	No clinically significant change in ABC pharmacokinetics.	Monitor for signs and symptoms of methadone withdrawal; some patients may need an increased methadone dose. No adjustment of ABC dose required.

(contd) Interaction between ARVs and methadone

ARV	Effect of ARV on methadone	Effect of methadone on ARV	Comments
Dolutegravir (DTG)	DTG has no clinically relevant effect on the pharmacokinetics of methadone. Co-administration of methadone (16–150 mg) and DTG (50 mg twice daily) had no effect on methadone C _{max} , and decreased AUC and C _{trough} by 2 per cent and 1 per cent, respectively.	Co-administration of methadone (16–150 mg) and DTG (50 mg twice daily) had no effect on methadone C _{max} , and decreased AUC and C _{trough} by 2 per cent and 1 per cent, respectively.	No dose adjustment is necessary for methadone or DTG.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Efavirenz (EFV)	Co-administration of EFV (600 mg once daily) with methadone (35–100 mg once daily, stable maintenance doses) decreased methadone AUC and C _{max} by 52 per cent and 45 per cent, respectively.	Unknown.	Patients should be monitored for signs of withdrawal and their methadone dose increased as required.
Nevirapine (NVP)	Co-administration decreases methadone AUC by ~40–65 per cent; narcotic withdrawal syndrome has been reported in patients treated with NVP and methadone concomitantly.	Not studied.	Methadone-maintained patients beginning NVP therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Protease inhibitors (PIs)			
Lopinavir/ritonavir (LPV/r)	Methadone AUC decreased by 53 per cent.	None reported.	Increase dose of methadone according to patients' withdrawal symptoms. Caution should be exercised when administering both drugs due to the risk of QT prolongation. ECG monitoring is recommended.
Saquinavir (SQV)	Co-administration with SQV/ritonavir decreased R-methadone AUC by 19 per cent. Co-administration is contraindicated in the European SPC due to potentially life-threatening cardiac arrhythmia (QT prolongation), but the US Prescribing Information advises caution and warns that the dosage of methadone may need to be increased.	A study found SQV AUC decreased 19 per cent and another study reported no change.	A more cautious approach is recommended. If co-administered, ECG monitoring is recommended. The dosage of methadone may need to be increased when co-administered with SQV/ritonavir.

Interaction between ARVs and buprenorphine

ARV	Effect of ARV on buprenorphine	Effect of buprenorphine on ARV	Comments
Nucleoside reverse transcriptase inhibitors (NRTIs)			
No significant interactions reported.			
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Efavirenz (EFV) and nevirapine (NVP)	Buprenorphine concentrations decreased but not significantly.	None reported.	No dose adjustment of EFV and NVP required.
Protease inhibitors (PIs)			
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.

Interaction between hepatitis C virus (HCV) antiviral agents (AVA) and methadone

HCV antiviral agents	Effect of HCV-AVA on methadone	Effects of methadone on HCV-AVA	Comments
Daclatasvir	Co-administration of methadone (40–120 mg once daily, individualized dose) and daclatasvir (60 mg once daily). There was no clinically relevant effect on concentrations of R-methadone (AUC, Cmax and Cmin increased by 8 per cent, 7 per cent and 8 per cent, respectively).	There was no clinically relevant effect on daclatasvir concentrations.	No dose adjustment of daclatasvir or methadone is required.
Sofosbuvir	Co-administration of sofosbuvir and methadone (30–130 mg/daily) had no significant effect on R-methadone (AUC increased by 1 per cent, Cmax and Cmin decreased by 1 per cent and 4 per cent) or S-methadone (Cmax, AUC and Cmin all decreased by 5 per cent).	Sofosbuvir is a prodrug and formation of its active metabolite is unlikely to be affected by comedication.	No dose adjustment of sofosbuvir or methadone is required.
Ledipasvir/sofosbuvir	Co-administration with ledipasvir/sofosbuvir has not been studied.	Not studied.	No a priori dose modification is recommended.
Ribavirin	No Data.	No Data.	No Data.
Velpatasvir	Not clinically significant.	Not clinically significant.	No interaction was observed between methadone and velpatasvir.

Interaction between hepatitis B virus (HBV) antiviral agents (AVA) and methadone

Tenofovir-DF (HBV)	No significant interaction observed.	No significant interaction observed.	No effect of Tenofovir-DF on methadone observed.
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Interaction between HCV AVA and buprenorphine

HCV antiviral agents	Effect of HCV-AVA on buprenorphine	Effects of buprenorphine on HCV-AVA	Comments
Daclatasvir	No negative interaction expected.		
Sofosbuvir	No negative interaction expected.		
Ledipasvir/sofosbuvir	Co-administration has not been studied, but based on limited data, a clinically significant interaction is unlikely.		
Ribavirin	Co-administration has not been studied, but based on metabolism and clearance, a clinically significant interaction is unlikely.		

Interaction between hepatitis B virus (HBV) antiviral agents (AVA) and methadone

Tenofovir-DF (HBV)	No negative interaction expected.
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Note: It appears no study has been undertaken of the interaction between methadone doses greater than 120 mg and drug interactions (AVA). However, a preliminary study proposed that HCV may alter methadone metabolism via HCV-associated hepatic inflammation, and this has been associated with a reduction in methadone dosage requirement.¹¹⁷⁶ Until further studies are undertaken, patients receiving methadone (> 120 mg) and treated with AVA for HCV should be observed for any potential adverse interactions.

The University of Liverpool, United Kingdom provides a clinically useful, reliable, comprehensive, up-to-date, evidence-based drug-drug interaction resource, freely available to health-care workers, patients and researchers. For the HIV Drug Interaction Checker, visit: <http://www.hiv-druginteractions.org/>

For the Hepatitis Drug Interaction Checker, visit: <http://www.hep-druginteractions.org> (Accessed 9 November 2021)

Interactions of methadone and buprenorphine with other medications

Rifampicin (TB)	Decrease in methadone level by 33–68 per cent; may induce symptoms of opioid withdrawal. Decreased plasma levels and withdrawal symptoms due to increased metabolism of buprenorphine are not known to occur.	Increase in methadone dose required if withdrawal symptoms present. If this is not done, patient may stop anti-TB medicines and use illicit drugs.
Sertraline (antidepressant)	Increase in methadone level by 26 per cent. Unknown in buprenorphine use.	Associated with cardiac rhythm disturbances; exercise caution when using with methadone. No dose adjustment required.

¹¹⁷⁶ Wu S-L, Wang S-C, Tsou H-H, Kuo H-W, Ho I-K, Liu S-W, et al. *Hepatitis C Virus Infection Influences the S-Methadone Metabolite Plasma Concentration*. PLoS ONE 8 (7): e69310. <https://doi.org/10.1371/journal.pone.0069310> . 2013.

(contd) Interactions of methadone and buprenorphine with other medications

Carbamazepine and phenytoin (anticonvulsants)	Decrease in methadone levels; may cause symptoms of methadone withdrawal. For carbamazepine, effects are unknown in buprenorphine use. For phenytoin, there is potential for interaction with limited supporting evidence in buprenorphine use.	Increase in methadone dose may be required; consider using sodium valproate as an alternative.
Fluconazole (antifungal)	Increase in methadone level by 35 per cent. For fluconazole, there is potential for interaction with limited supporting evidence in buprenorphine use.	Clinical significance unknown with methadone.

For further information:

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 PWID: drug interactions – module 8* (Jakarta, ASEAN/ USAID/WHO/FHI, 2007).

Appendix 4

Criteria for Opioid Dependence (ICD-10 and DSM 5)

DEPENDENCE (ICD-10)*	DEPENDENCE (DSM 5)*
Presence of three or more of the following in the last 12 months	Presence of at least two or more of the following in the last 12 months
1. Evidence of tolerance.	1. Taking more opioid drugs than intended.
	2. Tolerance for opioids.
2. A physiological withdrawal state when substance use has ceased or reduced.	3. Withdrawal symptoms when opioids are not taken.
3. A strong desire or sense of compulsion to take the substance.	4. Cravings for opioids.
4. Difficulties in controlling substance-taking behaviour in terms of its onset, termination or levels of use.	5. Wanting or trying to control opioid drug use without success.
5. Progressive neglect of alternative pleasures or interests, increased amount of time necessary to obtain or take the substance or to recover from its effects.	6. Failing to carry out important duties at home, work or school because of opioid use.
	7. Giving up or reducing other activities because of opioid use.
	8. Spending a lot of time obtaining, taking or recovering from the effects of opioid drugs.
6. Persisting with substance use despite clear evidence of overtly harmful consequences.	9. Continuing to use opioids despite use of the drug causing relationship or social problems.
	10. Knowing that opioid use is causing a physical or psychological problem but continuing to take the drug anyway.
	11. Using opioids even when it is physically unsafe.

* Adapted from WHO ICD-10 diagnostic guidelines for substance use disorders

+ Adapted from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, fifth edition, DSM-5™

Appendix 5

Clinical Opiate Withdrawal Scale (COWS)

For each item, write in the number that best describes the patient's signs or symptoms. Rate those only as they pertain to an apparent relationship to opiate withdrawal (for example, if heart rate is increased because the patient was jogging prior to assessment, the increase pulse rate would not add to the score).

Flowsheet for measuring symptoms over a period of time during methadone or buprenorphine induction:

Patient's Name : _____		Date : _____		
Methadone or buprenorphine induction :				
Enter scores at time zero, 30 min after first dose, 2 hours after first dose, etc.				
Times _____ / _____ / _____ / _____				
1. Resting Pulse Rate: (Record beats per minute) <i>Measured after patient is sitting or lying for one minute</i> 0 pulse rate 80 or below 1 pulse rate 81–100 2 pulse rate 101–120 4 pulse rate greater than 120				
2. Sweating: <i>Over past ½ hour not accounted for by room temperature or patient activity</i> 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face				
3. Restlessness: <i>Observation during assessment</i> 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/ arms 5 unable to sit still for more than a few seconds				
4. Pupil size: 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible				

<p>5. Bone or joint aches: <i>If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored</i></p> <p>0 not present</p> <p>1 mild diffuse discomfort</p> <p>2 patient reports severe diffuse aching of joints/ muscles</p> <p>4 patient is rubbing joints or muscles and is unable to sit still because of discomfort</p>				
<p>6. Runny nose or tearing: <i>Not accounted for by cold symptoms or allergies</i></p> <p>0 not present</p> <p>1 nasal stuffiness or unusually moist eyes</p> <p>2 nose running or tearing</p> <p>4 nose constantly running or tears streaming down cheeks</p>				
<p>7. GI Upset: <i>Over last ½ hour</i></p> <p>0 no GI symptoms</p> <p>1 stomach cramps</p> <p>2 nausea or loose stool</p> <p>3 vomiting or diarrhea</p> <p>5 Multiple episodes of diarrhea or vomiting</p>				
<p>8. Tremor: <i>Observation of outstretched hands</i></p> <p>0 No tremor</p> <p>1 tremor can be felt, but not observed</p> <p>2 slight tremor observable</p> <p>4 gross tremor or muscle twitching</p>				
<p>9. Yawning: <i>Observation during assessment</i></p> <p>0 no yawning</p> <p>1 yawning once or twice during assessment</p> <p>2 yawning three or more times during assessment</p> <p>4 yawning several times/minute</p>				
<p>10. Anxiety or Irritability:</p> <p>0 none</p> <p>1 patient reports increasing irritability or anxiousness</p> <p>2 patient obviously irritable anxious</p> <p>4 patient so irritable or anxious that participation in the assessment is difficult</p>				

11. Gooseflesh skin: 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection				
Total scores				
Observer's initials				

Score:

5–12 = Mild

13–24 = Moderate

25–36 = Moderately severe

more than 36 = Severe withdrawal

Source: Wesson, D. R., & Ling, W. *The Clinical Opiate Withdrawal Scale (COWS)*. J Psychoactive Drugs, 35(2), 253–9. 2003.

Appendix 6

Common adverse effects of methadone and buprenorphine

It is not uncommon for methadone or buprenorphine to have adverse effects. Patients should be educated on the potential side effects before the commencement of treatment. This will allow for early detection and management. Key adverse effects, common causes and suggested responses are as follows:¹⁷⁷

SIDE EFFECT	COMMON CAUSES	THINGS YOU CAN DO
Feeling drowsy after taking dose	<ul style="list-style-type: none"> Dose too high Other drug use (legal or illegal) 	<ul style="list-style-type: none"> Lower the maintenance dose and review other medications the patient may be taking
Withdrawal symptoms maximal before next dose	<ul style="list-style-type: none"> Dose too low Changes in legal or illegal drugs that patient may be using 	<ul style="list-style-type: none"> Raise maintenance dose Review other drugs patient is taking
Withdrawal precipitated by buprenorphine dose	<ul style="list-style-type: none"> Occurs early in treatment (or after absence from treatment) when buprenorphine dose administered soon after opioid use (e.g., heroin, methadone, morphine) 	<ul style="list-style-type: none"> Transient effect. Aim to prevent by patient education. Delay buprenorphine dose until patient experiencing opioid withdrawal. Discourage use of on-top heroin
Headache	<ul style="list-style-type: none"> Common in first week of buprenorphine treatment Other causes of headache 	<ul style="list-style-type: none"> Side effect is transient and generally mild. Consider aspirin or paracetamol
Nausea and vomiting	<ul style="list-style-type: none"> Common in early treatment 	<ul style="list-style-type: none"> Side effect usually transient (days). Avoid rapid dose increases Consider dose reduction if persistent
Constipation	<ul style="list-style-type: none"> All opioids have this effect Will be made worse by lack of dietary fibre, fluid intake or exercise 	<ul style="list-style-type: none"> Encourage fibre intake (fruit, cereals, vegetables), fluids, and regular exercise. Administer stimulant laxatives if necessary
Weight gain, particularly for women	<ul style="list-style-type: none"> Fluid retention caused by opioids – more likely on high doses Eating more while in treatment; high salt intake 	<ul style="list-style-type: none"> Lower dose Reduce fat and salt in diet, institute an exercise regimen

SIDE EFFECT	COMMON CAUSES	THINGS YOU CAN DO
Poor sleep	<ul style="list-style-type: none"> • Dose too low and causing withdrawal at night • Dose too late at night, causing stimulation at time of peak effects • Other drugs (particularly stimulants in the evening, such as coffee, nicotine and amphetamines) • General anxiety or irregular sleep pattern • Depressive illness • Central sleep apnoea 	<ul style="list-style-type: none"> • Review maintenance dose and review other medications • Explain importance of sleep patterns and routine
Amenorrhoea or oligomenorrhoea	<ul style="list-style-type: none"> • All have this effect • May be related to lifestyle, stressors, poor diet and general poor health 	<ul style="list-style-type: none"> • Periods may return after cessation of heroin use, or following withdrawal from opioids • Address other causes
Lowered sex drive	<ul style="list-style-type: none"> • More common with a high dose through effect on sex hormones • Can be many other psychological factors (such as anxiety, poor relationship with partner, etc.) 	<ul style="list-style-type: none"> • Review dose • Consider investigation for opioid-induced hypogonadism
Dental problems (specific to methadone)	<ul style="list-style-type: none"> • All opioids reduce saliva flow • Poor diet, dental hygiene 	<ul style="list-style-type: none"> • Encourage oral hygiene, dental floss and use of sugar free gum • Dental check-up • Reduce intake of sugary drinks and sweet food

Appendix 7

Risk assessment tool of providing take-away doses

CHECKLIST FOR ASSESSING APPROPRIATENESS OF TAKE-AWAY DOSES

Patient name: _____

Date of birth: / /

Mark each ☐ box that applies

Review date: / /

The supply of take-away doses is a significant clinical decision that requires thorough consideration of the risks and benefits. Prescribers should use this assessment tool when reviewing a patient to assess the appropriateness of take-away doses. Follow steps 1 to 4 in sequential order.

There are increased risk and safety concerns for the patient and others if ANY of the following contra-indications have been observed within the last three months:

1. ABSOLUTE CONTRA-INDICATIONS

Overdose of any substance reported	<input type="checkbox"/>
Reported diversion of doses to others, sharing or trading doses	<input type="checkbox"/>
No safe and secure storage facility available	<input type="checkbox"/>
Concerns about risk of harm to self or others	<input type="checkbox"/>

STOP: Do not supply take-away doses if any absolute contra-indications have been observed.

2. RELATIVE CONTRA-INDICATIONS

Attendance at medical/case manager reviews Irregular attendance missed >1 in 4 appointments	<input type="checkbox"/>
Missed doses Missed doses (confirmed with pharmacist) missed >1 dose per week	<input type="checkbox"/>
Provision of urine drug screens (UDS) UDS not provided on request or reveals unsanctioned drug use	<input type="checkbox"/>

(contd) 2. RELATIVE CONTRA-INDICATIONS

Unsanctioned use of other drugs Reported misuse of prescription medicines, alcohol or illicit drugs Evidence of recent injecting sites Intoxicated presentations at medical clinic	<input type="checkbox"/>
Concerns about misuse of take-away doses Reported use of take-away doses in advance Reported hoarding or 'stockpiling' of take-away doses Reported lost or stolen take-away doses	<input type="checkbox"/>
Accommodation No stable accommodation Persons with histories of drug misuse are present or likely to visit the home	<input type="checkbox"/>
Physical and mental state assessment Concerns about other medical condition (e.g., severe liver or respiratory disease)	<input type="checkbox"/>

CAUTION: If any relative contra-indications have been observed, prescribers should discuss the appropriateness of take-away doses.

3. REASONABLE NEED

A reasonable need for take-away doses should be established when considering take-away doses. At least one of the following should be present:

Work, study or family commitments where daily attendance is not possible	<input type="checkbox"/>
Living in a rural or remote area where daily travel is difficult	<input type="checkbox"/>
Significant medical condition restricting ability to attend on a daily basis	<input type="checkbox"/>
Urgent travel where alternative arrangements for supervised dosing cannot be arranged	<input type="checkbox"/>
Incentive and reward for stability and progress in treatment	<input type="checkbox"/>

CAUTION: If no reasonable need is established, prescribers should discuss the appropriateness of take-away doses.

Ensure steps 1 to 3 of the assessment have been completed before proceeding to step 4.

4. CONTINUOUS PERIOD OF STABILITY

Supply of take-away doses may be considered after a continuous period of stability in treatment. The following schedule is recommended:

METHADONE	
< 3 MONTHS	No take-away doses
3–6 MONTHS	0–2 take-away doses per week
> 6 MONTHS	0–4 take-away doses per week, with no single supply exceeding 3 take-away doses

BUPRENORPHINE/NARLOXONE*	
< 2 WEEKS	No take-away doses
2 WEEKS–2 MONTHS	0–2 take-away doses per week
2–6 MONTHS	0–5 take-away doses per week
> 6 MONTHS	0–6 take-away doses per week

CAUTION: Prescribers considering varying from this schedule are strongly advised to discuss with the MAT team regarding the patient's stability in treatment and suitability for take-away doses. Mutually agreed treatment decisions should be reached and documented.

* Take-home doses of buprenorphine-mono are generally not recommended as the risk of the patient injecting their buprenorphine is high.

Comments: (e.g., overall assessment, matters for follow-up at the next review)

Review conducted by: _____ (prescriber)

Date of next review: / /

Appendix 8

Modified Finnegan Scale for Neonates

This scale is used neonatal opioid withdrawal. Infants of mothers known or suspected to be PWUD and are showing signs of withdrawal should be scored every four hours. The scoring should be applied in a consistent manner by staff that have some experience in treating such infants. Do not assume that all of the following symptoms are part of drug withdrawal. Some symptoms, such as fever or seizures, could be due to sepsis, which should be excluded first with appropriate tests.

SYSTEMS	SIGNS AND SYMPTOMS	SCORE
Central nervous system disturbances	High-pitched cry	2
	Continuous high-pitched cry	3
	Sleeps <1 hour after feeding	3
	Sleeps <2 hours after feeding	2
	Sleeps <3 hours after feeding	1
	Mild tremors disturbed	1
	Moderate-severe tremors disturbed	2
	Mild tremors undisturbed	3
	Moderate-severe tremors undisturbed	4
	Increased muscle tone	2
	Excoriation (specify area)	1
	Myoclonic jerks	3
	Generalized convulsions	5
Metabolic/vasomotor/respiratory disturbances	Fever (37.3-38.3 deg C)	1
	Fever (>38.3 deg C)	2
	Frequent yawning (>3-4 times)	1
	Nasal snuffiness	1
	Sneezing (>3-4 times)	1
	Nasal flaring	2
	Respiratory rate > 60/min	1
	Respiratory rate > 60/min + retractions	2
Gastrointestinal disturbances	Excessive sucking	1
	Poor feeding	2
	Regurgitation	2
	Projectile vomiting	3
	Loose stools	2
	Watery stools	3

Infants scored three consecutive abstinence scores averaging more than 8 (e.g., 9-7-9) or ≥ 12 for two scores require treatment. The scoring interval should every four hours until the infant has been stabilized. Reference: Finnegan L. *Drug Dependence in Pregnancy*. London, Castle House Publications. 1980.)

Appendix 9

List of contributors

In partnership with the Government of Nigeria, UNODC is implementing the large-scale, EU-funded project “Response to Drugs and Related Organized Crime in Nigeria”. The project aims to support Nigeria’s efforts in fighting drug production, trafficking and use, and curbing related organized crime. The project adopts a balanced approach to drug control, with equal attention paid to drug interdiction and drug demand reduction, including drug prevention, treatment and care (DPTC).

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