

Module 4

Managing Opioid Dependence

Treatment and Care for
HIV-Positive Injecting Drug Users



Module 4

Managing opioid dependence

Participant Manual

2007



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Module 1: Drug use and HIV in Asia: participant manual

Module 2: Comprehensive services for injecting drug users – participant manual

Module 3: Initial patient assessment – participant manual

Module 5: Managing non-opioid drug dependence – participant manual

Module 6: Managing ART in injecting drug users – participant manual

Module 7: Adherence counselling for injecting drug users – participant manual

Module 8: Drug interactions – participant manual

Module 9: Management of coinfections in HIV-positive injecting drug users – participant manual

Module 10: Managing pain in HIV-infected injecting drug users – participant manual

Module 11: Psychiatric illness, psychosocial care and sexual health – participant manual

Module 12: Continuing medical education – participant manual

Trainer manual: Treatment and care for HIV-positive injecting drug users

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Abbreviations and acronyms

| | |
|--------|--|
| AA | Alcoholics Anonymous |
| ACTH | adrenocorticotrophic hormone |
| ADH | antidiuretic hormone |
| AIDS | acquired immunodeficiency syndrome |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| ASEAN | Association of Southeast Asian Nations |
| ATS | amphetamine-type stimulants |
| BCC | behaviour change communication |
| CDC | Centers for Disease Control and Prevention (US Government) |
| CNS | central nervous system |
| DOTS | directly observed treatment, short course |
| EFV | efavirenz |
| FBE | full blood examination |
| FHI | Family Health International |
| FSH | follicle-stimulating hormone |
| HIV | human immunodeficiency virus |
| ICD-10 | International Classification of Diseases, 10th revision |
| IDUs | injecting drug users |
| LAAM | levo-alpha-acetylmethadol |
| LFT | liver function tests |
| LH | luteinizing hormone |
| MMT | methadone maintenance treatment |
| NGO | nongovernmental organization |
| NSAID | non-steroidal anti-inflammatory drug |
| NVP | nevirapine |
| OST | opioid substitution therapy |
| PLWHA | people living with HIV and AIDS |
| TB | tuberculosis |
| UDS | urine drug screen |
| UNODC | United Nations Office on Drugs and Crime |
| USAID | United States Agency for International Development |
| WHO | World Health Organization |

Opioid use, opioid dependence and withdrawal syndromes

OVERVIEW



Objectives:

By the end of the session participants will be able:

- To understand the social, psychological and biological reasons for drug use
- To describe the features of drug use and understand the particular features of opioids and the neurobiology of their use
- To understand the “harms” related to drug use
- To understand and recognize the difference between drug use and dependence
- To understand and recognize the features of the opioid dependence and withdrawal syndromes



Time to complete session:

1 hour 45 minutes



Session content:

- Drug use in society – how it starts and continues
- ICD-10 diagnostic guidelines
- The natural history of opioid dependence and associated harms
- Switching to injecting drug use
- Heroin injection-related harms
- Reduction of harm associated with injecting drug use



Training materials:

- PowerPoint presentation 4.1: Managing opioid dependence: opioid use, opioid dependence and withdrawal syndromes
- Sub-module 4.1: Opioid use, opioid dependence and withdrawal syndromes

DRUG USE IN SOCIETY

There is documentary evidence for thousands of years of the use of a variety of recreational drugs in most cultures. By reflecting on our personal experiences of initiation of the use of legal recreational drugs – smoking tobacco, drinking coffee and alcohol – it is possible to gain insight into the initiation of illicit drugs.

The reasons for initiation of drug use include the influence of peer pressure, the desire to appear “mature” or like a mentor or idol, the perception that it is a “normal” cultural or social activity, to relieve stress or anxiety, as self-medication, in response to advertisements or cinema images for experimentation, or as an act of rebellion.

Having initiated drug use, the continuation of that use, particularly in the context of associated problems, is driven by complex functional and dependence issues. For example, most continued licit and illicit drug use can be described as a response to peer pressure, a habit or craving, for their properties of stimulation or relaxation, to avoid withdrawal, for social enjoyment or inclusion, to “take a break”, for pain relief or to forget problems, inability to stop, or for the pleasure they provide.

Exposure to drug use

Exposure of a naive individual to an addictive drug elicits a response that is a complex interplay of physical and environmental factors with some individuals refraining from further use, others sustaining recreational or functional use, and a minority progressing through use to a dependence syndrome. This divergence of outcomes from exposure to the same level of initial exposure is observed in all cultures and in all animal models of drug dependence.

Drug “use” versus “dependence”

Clearly, few users of any drug become dependent. The estimated proportion of exposed individuals who become dependent on drugs are: nicotine >30%, heroin 25%, cocaine >15%, alcohol 10–15%, marijuana <5% (controversial) and for amphetamine-type stimulants (ATS) the proportion is unclear (though it is certainly more for crystal methamphetamine). These figures are influenced to an unclear degree by the legal sanctions placed on the use of that drug and the period of exposure.

To achieve an adequate understanding of problematic and dependent drug use, it is useful to view it as a typical chronic “health impairment” – a chronic relapsing condition characterized by exacerbations and remissions with a number of predisposing conditions and a cycle of evolution and resolution.

ICD-10 DIAGNOSTIC GUIDELINES

There are two internationally accepted diagnostic criteria that cover drug dependence: the tenth revision of the *International Classification of Diseases (ICD-10)* published by the World Health Organization (WHO) in 1992, and the fourth edition of the *Diagnostic and statistical manual of mental disorders (DSM-IV)* published by the American Psychiatric Association in 1994.

ICD-10 defines “dependency syndrome” as:

... a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had a greater value (WHO Expert Committee on Drug Dependence, 1998).

A definite diagnosis of dependence syndrome should be made only if three or more of the following have been present together at some time during the previous year:

- Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses
- A physiological withdrawal state when substance use has ceased or has been reduced, as evidenced by the characteristic withdrawal syndrome for the substance, or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms
- A strong desire or sense of compulsion to take the substance
- Difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use
- Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects
- Persisting with substance use despite clear evidence of overtly harmful consequences, including depressive mood states consequent to periods of heavy substance use or drug-related impairment of cognitive functioning.

The “life cycle” of dependent drug use appears to be predetermined by the drug itself with some evidence for spontaneous remission (for example, after 10–15 years with heroin, approximately 5 years with amphetamines, and more than 40 years with cigarettes).

There is a strong association between relapse to problematic drug use and geographical or social cues.

THE NATURAL HISTORY OF HEROIN DEPENDENCE

Opiate dependence (like that of other addictive drugs) is a chronic relapsing and remitting condition with periods of uncontrolled use and others of abstinence. The dependence usually starts several years after first heroin use, is independent of the mode of drug administration, and displays a 2–5% spontaneous remission rate per year. There is a finite mortality rate of usually 1–2% per year from a combination of drug overdose, drug use-related illness and violent death.

In a number of studies in recent years, the 10-year outcomes of treatment seekers in the USA were broadly: 50% still using and/or imprisoned, 30% abstinent, and 20% dead. In addition, investigators of long-term outcomes of dependent heroin users have observed that most stop heroin use by their mid-30s to mid-40s.

Neuroadaptation

With repeated administration of an addictive drug, a normal physiological adaptation leads to a decrease in drug receptor density, a change in receptor morphology and drug receptor desensitization. These changes in the brain are currently understood to be responsible for the observed tolerance to increasing doses of the addictive drug and for the withdrawal syndrome observed on its cessation.

A scientific study compared recovering addicts who had stopped using cocaine for more than one year with people who had no history of cocaine use. The study observed, using positron emission tomography (PET), how just the *mention* or *sight* of items associated with drug use caused activity in the reward area of the brain in ex-addicts, associated with the craving or desire to use drugs.

For this study, brain scans were performed while subjects watched two videos. The videos compared the impact of a non-drug presentation, with images of nature – mountains, rivers, animals, flowers and trees – with a second presentation showing cocaine use and drug paraphernalia, such as pipes and syringes.

The study results clearly showed that even after a year of abstinence, those subjects who had been dependent showed very different responses to the two videos in contrast to those subjects who had never been dependent. The findings have been reproduced with heroin and cigarettes and are specific for images of the drug of dependence.

It is unclear how long the *changed brain* remains abnormal in its response to these drug-specific cues, though it does appear that the changes fade over many years. Certainly, it seems clear that these long-standing focal brain changes are important for an understanding of drug dependence, relapse and the response of an abstinent ex-user to environmental cues.

SWITCHING TO INJECTING DRUG USE

This more harmful form of drug use typically (but not always) starts with richer groups and shifts to poorer sectors of society. It is a behaviour change associated with mobile populations and drug transit routes, and is usually associated with societies in the process of rapid social and economic change.

Injecting use has also been associated with access to higher quality (though more expensive) drugs and to increasing drug prices or to the development of individual tolerance. Most of all, it is a phenomenon of the drug-using subculture where peer behaviours and myths have the most impact.

HEROIN INJECTION-RELATED HARMS

A small group discussion of the potential harms associated with heroin use will allow participants to share ideas and preconceptions about drug users and the risks they take. The harms of drug use extend well beyond the personal and physical, and a good discussion session will usually produce a comprehensive list that includes biological, psychological, social and economic harms.

Harms associated with injection use include: bloodborne infection from shared equipment (hepatitis, HIV, malaria), systemic infections (endocarditis, fungal abscess, osteomyelitis) and local infection from poor technique or hygiene. Also, there is the potential harm of opioid overdose including death. Death and injury from suicide, accidental death and violence are also more common among drug users.

Social and personal costs include: crime, theft, imprisonment and drug importation, manufacture and distribution syndicates and sex work. Stigma includes the drug user, his/her family and the whole community.

Financial costs include poverty and legal problems. Costs to the community are substantial and include security, policing, prisons, insurance, customs, corruption of officials and distortion of the economy towards illicit trade.

Participants should also discuss the causes of drug-related harms and actions that may be taken to mitigate them.

REDUCTION OF HARM ASSOCIATED WITH INJECTING DRUG USE

Reduction of IDU-related harm is one component of a comprehensive strategy to minimize the harm of drug use, and includes supply and demand reduction. Reduction of drug-related harm aims to reduce harm to the *individual* and *the community*. In the hierarchy of stated goals, “cure” (abstinence) is the ideal, but reducing levels of drug use and changing high-risk behaviours are equally important goals.

Reduction of harm is a common paradigm for medical care, particularly with licit substance use. Cigarette smoking leads to the development of asthma; excessive food intake to obesity, diabetes and hyperlipidaemia.

Health professionals should not expect that IDUs’ harmful behaviour will cease in response to medical advice, but over time, small changes may occur with information, persuasive advice, insight and an enabling environment.

SUMMARY

- Drug use has a long history in Asia.
- Most drug use does not lead to dependence.
- Drug dependence is a chronic relapsing syndrome.
- There are social, psychological and biological reasons for drug use.
- The harms associated with drug use are not in the main related to the drugs themselves.

To adequately care for those with problematic drug use, health professionals need to develop an understanding of the social, psychological and biological reasons for drug use and an awareness of the features of opioid use and dependence. In addition, health professionals need to be aware of the harms caused by heroin and other opioid use and some of the means for reducing such harm.

EXERCISE 4.1

CASE STUDIES

Case study 1

Please read the following case study.

Tan, a 26-year-old heroin user, presents to his health centre doctor inquiring about treatment.

Tan has attended this clinic occasionally over the past three to four years, attempting outpatient drug withdrawal several times. On one occasion two years ago he entered methadone maintenance treatment, but dropped out after two weeks. He last attended the health centre eight months ago for an outpatient withdrawal.

Tan describes first smoking heroin six years ago, and first regular injecting use five years ago. He states he is currently injecting heroin on average three times a day, using heroin worth US\$ 10 each day. He states he remained “clean” for approximately three weeks after the last heroin withdrawal, then began use again – escalating to this current level of use about five months ago. This is a recurring pattern for Tan, with relapses soon after each withdrawal attempt.

Tan smokes 20 cigarettes per day, but describes no other regular drug use. He has no other significant medical or psychiatric conditions. He lives with friends in a share house, one of whom also uses heroin. He is casually employed stacking shelves at a supermarket, where several of his friends also use heroin. He is not in a relationship, but maintains regular contact with his mother, who has suggested he enter treatment.

The doctor is encouraged that finally Tan is thinking more about longer-term treatment than simply withdrawal. The doctor had for a long time been suggesting that Tan enter some form of longer-term treatment, but in the past Tan has been reticent about counselling, been unprepared to enter long-term rehabilitation, was not keen on Narcotics Anonymous, and was still wary of methadone maintenance treatment.

Small group discussions:

Break up into small groups to discuss these questions. Choose a speaker from your group who will report back to the class.

- 1. Identify the features of drug use.**
- 2. Identify the characteristic features of opioid dependence.**
- 3. What are the possible harms?**

Case study 2

Please read the following case study.

Ruli is a 24-year-old heroin user with a three-year history of regular heroin injection. He presents to his doctor seeking “help” about a recently infected forearm injection site.

The doctor treats the local infection with a prescription for antibiotics and recommends that the patient stop his injecting drug use. Ruli appears somewhat ambivalent about stopping, but is prepared to “go along” with the doctor and offers no objection when the doctor makes an appointment for him to attend the local drug treatment centre in four days for an assessment.

A week later, Ruli presents again to the doctor seeking another prescription for antibiotics as the infection has not entirely resolved. It is clear that Ruli has continued his injecting drug use and that he had not kept his appointment with the drug treatment centre withdrawal unit. The doctor is frustrated, wondering why she bothered taking the extra time at the last appointment to call the drug treatment centre in the first place. However, she does not express her disappointment to Ruli and provides another prescription for antibiotics. She concludes the consultation with an offer for Ruli to come back again to see her if he wants treatment in the future.

Six weeks later Ruli presents again, still somewhat ambivalent about stopping his drug use altogether, but his heroin use has escalated in recent weeks. He is now facing serious financial problems and is about to be evicted. Going through the options, Ruli agrees that he cannot keep using heroin like he has been and that the situation is out of control. The doctor again suggests an inpatient “detox”. He agrees to heroin withdrawal medication, but does not want to go to an inpatient unit because “it is full of junkies”. He begins an outpatient withdrawal regimen with the doctor, who also engages a local drug treatment NGO to provide some counselling during and after the withdrawal.

Small group discussions:

Break up into small groups to discuss these questions. Choose a speaker from your group who will report back to the class.

1. **Identify the features of drug use.**
2. **Identify the characteristic features of opioid dependence.**
3. **What are the possible harms?**

Evaluation and treatment of opioid dependence and withdrawal syndromes including OST

OVERVIEW



Objectives:

By the end of the session participants will be able:

- To understand and recognize the features of opioid intoxication and withdrawal syndromes
- To evaluate clients for treatment and commence withdrawal or maintenance treatment
- To understand the basic components of successful OST.



Time to complete session:

1 hour 30 minutes



Session content:

- Effects of heroin and other opioids
- Effects of opioid withdrawal
- Working with drug users
- Opiate treatment cascade
- Objectives of withdrawal services
- Objectives of substitution maintenance treatment
- Opioid substitution therapy (OST)
- Key features of OST assessment
- Side-effects of OST
- Methadone substitution therapy
- OST in Asia



Training materials:

- PowerPoint presentation 4.2: Managing opioid dependence: evaluation and treatment of opioid dependence and withdrawal syndromes including OST
- Sub-module 4.2: Evaluation and treatment of opioid dependence and withdrawal syndromes including OST

EFFECTS OF HEROIN AND OTHER OPIOIDS

By reflecting on your experience with common therapeutic opioids, it is possible to construct a picture of the physiological impact of heroin use and the appearance of opioid intoxication.

All the opioid agonists have these effects in common:

- **Central nervous system:** analgesia, euphoria, pupillary constriction, sedation, suppression of cough reflex, respiratory depression, coma and death
- **Gastrointestinal system:** nausea and vomiting, constipation, reduced gastric emptying, increased tone of the pyloric sphincter and sphincter of Oddi (biliary duct spasm)
- **Endocrine:** reduced follicle-stimulating hormone (FSH)/luteinizing hormone (LH), amenorrhoea, decreased ejaculation and libido, elevated prolactin level and galactorrhoea, decreased testosterone, impotence and gynaecomastia in men
- **Skin:** itching, sweating, rash including urticaria, dry mouth, skin and eyes
- **Urinary:** urinary retention, inhibition of urinary reflex and difficulty in passing urine
- **Cardiovascular:** bradycardia, orthostatic hypotension

EFFECTS OF ACUTE OPIOID WITHDRAWAL

By referring to the physiological effects of opioids and expecting an opposite mechanism, it is possible to anticipate the likely physiological effects of acute opioid withdrawal. Most opioids have a short duration of action in terms of hours and, with the exception of methadone, have a withdrawal syndrome measured in days (usually less than five).

All the opioid agonist have these withdrawal effects in common:

- **Central nervous system:** pain and muscle cramps, dysphoria, restlessness, craving for opioids, insomnia, pupillary dilatation, anxiety and irritability, yawning
- **Gastrointestinal system:** nausea and vomiting, diarrhoea, bowel cramps
- **Endocrine:** increased libido, restoration of potency
- **Skin:** sweating, piloerection, rhinorrhoea, increased lacrimation
- **Cardiovascular:** hypertension, tachycardia

WORKING WITH DRUG USERS

For this socially unacceptable and marginalized population, experience over four decades has identified what works – engagement. For the health professional, engagement consists of a constellation of attitudes and behaviours, including confidentiality, empathy and a non-judgemental approach. The health professional accepts the patient's autonomy to make decisions (both good and bad ones), uses adult learning principles for information transfer (experience and mistakes), and works with the patient to achieve outcomes: "How can the patient be helped to achieve his/her goals?"

OPIATE TREATMENT CASCADE

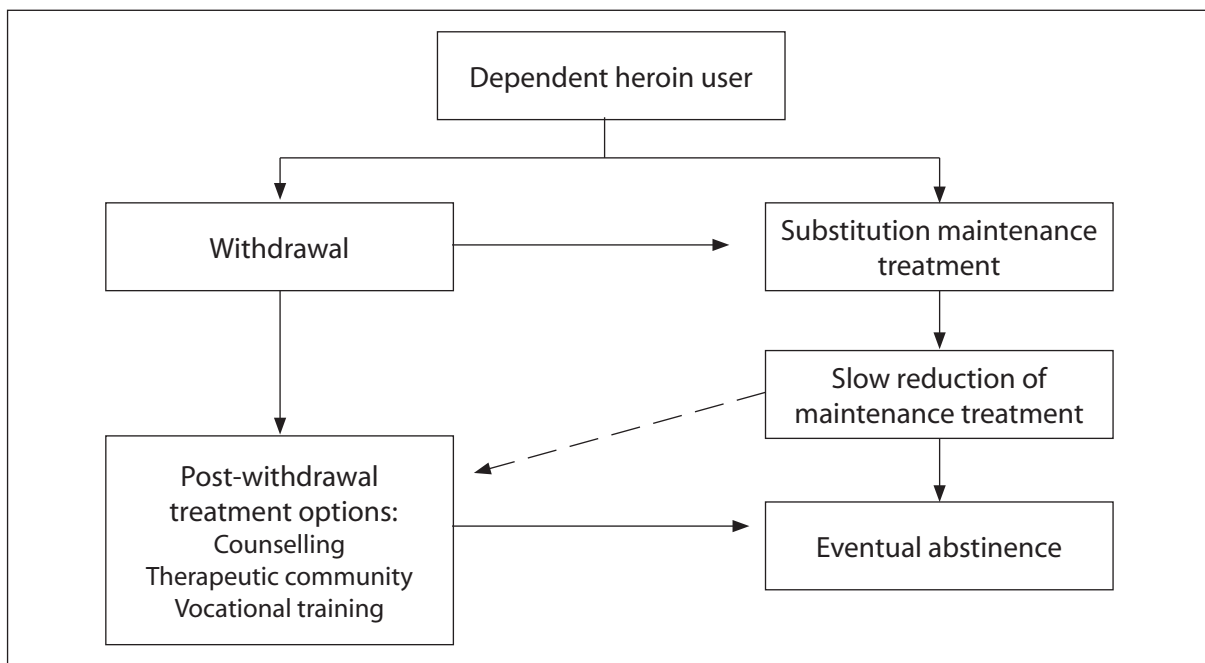
Supported by experiential evidence, a graded cascade of treatment interventions has been created. The likelihood of success increase and the risk of relapse decreases as one goes further down the cascade.

- Attempted self-cessation of drug use
- Counselling

- Medicated detoxification (withdrawal)
 - ◆ Outpatient
 - ◆ Home
 - ◆ Inpatient
- Relapse prevention
 - ◆ Naltrexone
 - ◆ Narcotics Anonymous
 - ◆ Residential rehabilitation
 - ◆ Mandated treatment (as in prison)
- Maintenance pharmacotherapies
 - ◆ Methadone /buprenorphine/levo-alpha-acetylmethadol (LAAM)
- “Geographical” – lifelong move

Also, interventions lower down the cascade are for a substantially longer duration, a factor which has been consistently shown to impact positively on treatment outcome. The ability of a treatment intervention to continue to engage the patient is a measure of its likely efficacy. The shorter the duration of drug treatment, the lower its likely treatment efficacy.

Figure 1. Treatment pathways for dependent heroin users



This diagram is an attempt to map out the pathways that a dependent drug user needs to pass through on the way to sustained abstinence or as a way of engaging in other longer-term treatment options such as opioid maintenance treatment (Figure 1). Most drug users plot a complicated path through treatment of recurrent failed attempts at many methods before finally settling on a solution that appears to meet their needs.

What is less clear from the diagram is the vastly different time-frames required for the different components. For example, substitution maintenance and slow reduction of maintenance programmes are of some years' duration while withdrawal programmes are measured in days.

OBJECTIVES OF WITHDRAWAL SERVICES

While withdrawal is not an effective treatment for opioid dependence, this short-term intervention has some benefit in allowing the drug user to regain some control and insight into the dependent nature of their relationship with the drug.

Cessation aims to alleviate the discomfort of drug withdrawal, prevent complications of self-managed withdrawal, prevent or treat destabilizing medical and psychiatric conditions, prevent polydrug overdose, intervene in social crises, interrupt a pattern of heavy and regular drug use, and finally to facilitate linkage with post-withdrawal treatment options.

Note: Withdrawal is not a “cure” for heroin dependence.

Components of withdrawal services

Comprehensive drug treatment services offering drug withdrawal should offer assessment, supportive care and counselling, a safe environment, provision of information, monitoring of the client’s physical and psychiatric condition, appropriate medications and linkages to post-withdrawal options.

In some countries withdrawal services exist only where it is necessary to stabilize clients before entry into longer treatment options (therapeutic communities, prison, hospital).

Use of medications in opioid withdrawal

The prescription of medications for the symptomatic treatment of opioid withdrawal has attracted considerable adverse attention and controversy. Opioid withdrawal is not a life-threatening condition, so prescribers must take care to “do no harm”. Medications include three broad groups:

- Opioid substitutes, controlled and weaned over a short period:
 - ◆ Methadone, buprenorphine, codeine, opium, dextropropoxyphene
- Symptomatic treatment:
 - ◆ Clonidine, benzodiazepines, loperamide, non-steroidal anti-inflammatory drugs (NSAIDs)
- Accelerated withdrawal using opioid antagonists (controversial):
 - ◆ Naltrexone, naloxone, deep sedation (benzodiazepines)

All withdrawal treatments are for symptomatic relief and none have been shown to have good long-term outcomes. Some withdrawal treatment regimens are associated with treatment mortality and all are associated with increased post-withdrawal mortality from rebound illicit opiate use in the presence of decreased tolerance.

Methadone has higher completion rates and better symptom control than buprenorphine, which in turn is much better than codeine or opium tincture. What is also becoming clear is that buprenorphine has some safety advantages over methadone and other opioids for short-term outpatient treatment of withdrawal. However, there is still a need to take great care with outpatient prescribing of benzodiazepines and other opiates.

Post-withdrawal interventions

Support is a very important aspect of successful drug withdrawal treatment, in addition to opioid substitution therapy (OST). It involves counselling (supportive, behavioural, cognitive and dynamic models) and providing the options of residential rehabilitation or a therapeutic community, self-help groups (Narcotics Anonymous, Rational Recovery), and provision of naltrexone (opioid

antagonist that can reduce craving and block the effects of additional heroin use; requires daily dosing and is effective in those who take it, but has an extremely high drop-out rate).

The addition of non-drug-related services, such as offering employment or vocational training, education and socialization outside of the user's previous drug culture, has been found to be of additional benefit.

OBJECTIVES OF SUBSTITUTION MAINTENANCE TREATMENT

Long-term OST attempts to reduce heroin and other drug use, mortality and transmission of bloodborne viruses; improve the patient's general health and well-being (psychosocial functioning) and reduce drug-related crime.

All studies of methadone treatment in the past four decades have documented, with varying efficacy, the ability of maintenance treatment to achieve these objectives.

Overview of substitution maintenance treatment

OST involves the provision of a long-acting opioid (e.g. methadone, buprenorphine) which enables the patient to cease or reduce their heroin use and related harmful behaviours. It is a long-term treatment approach (a number of years) which provides the opportunity for patients to distance themselves from a drug-using lifestyle and to re-enter "normal" society. By controlling drug craving and opioid use, it allows slow neurobiological recovery to occur.

The combination of medication and psychosocial services repairs the damage to the client's psychology and socialization caused by years of illicit drug use and exclusion from mainstream culture.

Table 1: Comparing treatments for opioid dependence

| Intervention | Effects on heroin use, retention at one year | Mortality | Goal |
|-----------------------------------|---|--------------------------|--|
| None | 5–10% long-term abstinence | ~2%/year | "Drug free" |
| Withdrawal | <5% long-term abstinence | ~2%/year ↑ after this | "Drug free" |
| Methadone maintenance | 50% retention @1 year 25% no heroin use @ 1 year | 4–10-fold reduction | Rehabilitation and long-term retention |
| Naltrexone maintenance | <20% retention 6/12 Most "drop-outs" relapse before 1 year | ~2%/year or more | "Drug free" |
| Residential rehabilitation | Progressive drop-out ++, motivation associated with external pressure. <15% still in treatment. <i>Highly selected.</i> | Unknown but may ↑ | "Rehabilitation" and "drug free" |

Source: Adapted from *Methadone Training Workshop for medical practitioners*

OPIOID SUBSTITUTION THERAPY (OST)

More than four decades of research on oral methadone liquid and nearly 15 years on sublingual buprenorphine tablets supports the use of these methods for the long-term maintenance treatment of opioid dependence.

Effectiveness of methadone treatment

Some of these study findings (DASA-NYC, 1991) are that MMT reduces property theft by 64%, overall arrests by 54%, drug offence arrests by 54%, emergency room visits by 65%, psychiatric hospitalizations by 55% and medical hospitalizations by 59%.

In 2003 a Cochrane review (Mattick et al. 2003) was conducted on 13 randomized controlled studies comparing the use of long-term methadone versus long-term buprenorphine for treatment efficacy. The conclusions were that the two drugs were similarly effective in treating heroin dependence, with methadone significantly more effective in suppressing heroin use (specifically at high doses) and that methadone was significantly more effective in retaining patients in the programme.

Cost-effectiveness of methadone

A United Kingdom (UK) National Treatment Outcome study (Gossop et al. 2005) found that for every pound invested in treatment, there is a return of three pounds because of reduced judicial costs to the justice system.

There is also an international consensus that OST saves the community between *7 and 10 times* the programme costs incurred due to legal law enforcement, incarceration, health care, social services, insurance premiums and payout expenses, customs and premature deaths.

Eligibility for OST

The minimum requirements to enter OST are that the client should be opiate dependent, give informed consent and satisfy local requirements (for example, more than six months of dependent use, at least one previous withdrawal attempt and able to travel daily to the dispensing site).

Some clients who present with co-morbid medical conditions are high priority for treatment, including HIV-positive heroin users requiring antiretroviral (ARV) drugs, pregnant heroin users, and those with TB requiring DOTS.

There are no fixed exclusion criteria (apart from not wanting maintenance treatment), but some co-morbid conditions require extra care when commencing substitution treatment (particularly with methadone). These conditions include:

- High-risk polydrug users
- Heroin users with a low level of neuroadaptation or a short duration of use
- Less than 18 years of age (for consent reasons)
- Psychiatric conditions
- Acute medical conditions (severe hepatic disease, respiratory illness or head injury)
- Chronic pain condition
- Personality disorder

Most of these conditions respond well to methadone treatment but require additional expertise during assessment and maintenance.

Pharmacology of methadone

Methadone is a synthetic, readily soluble opioid that is well-absorbed orally. The time course of its effects: onset of action at 30–60 minutes after dosing with a peak effect after 2–6 hours, and

therapeutic effects for 15–30 hours depending on the dose and hepatic metabolism. The half-life of methadone is 20–24 hours with *steady state equilibrium achieved only after 5 half-lives (5 days)*.

Methadone is metabolized by the hepatic cytochrome P450 system and is impacted by a number of important drug interactions, individual variation and disease states. In particular, it interacts with ART (nevirapine and efavirenz) and TB (rifampicin) medications.

Pharmacology of buprenorphine

Buprenorphine is another more recently developed synthetic (partial agonist) opioid that is poorly absorbed orally, heavily influenced by first-pass liver metabolism, and is taken as a sublingual preparation. The time course of its effects: onset of action 15–30 minutes after dosing with a peak after 1–4 hours, and therapeutic effects for 8–72 hours depending on the dose. Its half-life is very variable due to the ceiling effect of the drug and varies from 12–36 hours depending on the dose. Generally, *steady state equilibrium occurs after 5 half-lives (3–5 days)*.

Buprenorphine is also a partial opiate antagonist due to its high receptor affinity and weak opioid effect. It is metabolized by hepatic enzymes and conjugation with little impact caused by drug interactions, individual variation or disease states.

Commencing OST

The complexity of initiating OST involves balancing heroin withdrawal symptoms and the starting dose of the replacement opioid. The rationale for the low starting dose of methadone is to avoid death due to cumulative sedative overdose, which is more common in the first 10 days of OST. It is important to identify contributors to risk at starting (other drug use, chaotic heroin use, medical or psychiatric conditions) and to assess the level of neuroadaptation (decide high/medium/low dependence).

Buprenorphine is started at a low dose to avoid precipitated withdrawal from its partial opioid antagonist action. The starting dose of both methadone and buprenorphine is decreased in the presence of polydrug use.

It is vital to explain the features of the OST programme to the client, including: the rationale for the low starting doses and slow dose methadone increases; the contributors to risk at start of therapy; and the cumulative effect of methadone over a number of days. The client should also be cautioned about using other drugs due to the potential for sedative effects, delayed onset of methadone effects, and risk of continued heroin use and escalation of opioid tolerance. The side-effects of methadone and buprenorphine should be discussed (preferably with the provision of written literature about OST) and the client should be allowed to ask other questions.

Initiating treatment with methadone

Start with low doses of methadone according to the level of neuroadaptation (low 15–20 mg; medium 20–25 mg; High 25–30 mg) and review the patient frequently, titrating the dose carefully every few days to 60–120 mg per day.

“Start low, go slow and aim high.”

Initiating treatment with buprenorphine

Start with low doses of buprenorphine according to recent opiate use. Usually, 4–6 mg is given at least 6 hours and preferable 12 hours after last heroin use *to avoid precipitated withdrawal*. Review the patient frequently and titrate the dose carefully and quickly to 12–20 mg per day.

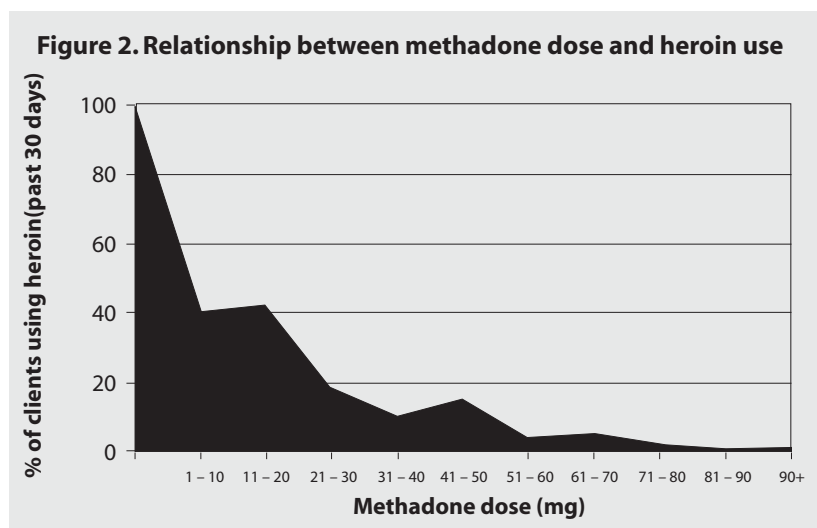
“Start low, go fast and aim high.”

Titration doses

The dose of methadone should be increased every 3–5 days (steady state). More rapid dose increases can result in methadone accumulation, toxicity and death due to overdose. The dose of buprenorphine should be increased after 6–8 hours with dose adjustments possible twice daily until the patient is stable.

An increase of 5–10 mg in the dose of methadone each time may be safe if the patient is still clearly undermedicated, but dose increases of more than 10 mg at a time are not safe, with a recommended maximum increase of 30 mg in any week. Buprenorphine increases of 4–6 mg per day are safe.

It is important to only increase the OST dose after reviewing the patient and if is clinically indicated (i.e. when the client is in withdrawal, still using heroin, still thinking or dreaming of using heroin and unable to say no when heroin is offered).



Source: National Library of Medicine. Adapted from Ball and Ross, 1991

KEY FEATURES OF OST ASSESSMENT

The assessment process should be used not only to gather clinical data to safely initiate OST, but also to establish a rapport with the client, engage him/her in the treatment process and facilitate the creation of a treatment plan. The presenting problem is an important signal to the way rapport may be established, and it is always important to address the presenting problem, even though it may be minor compared with the harm of the drug use.

It is necessary to assess the use of all drug classes (quantity, frequency, route of administration and duration of use) to assess the severity of dependence and level of neuroadaptation to each. The collection of information on risk practices and other co-morbid conditions impacting on treatment is important for taking a decision regarding the initial dose of OST (drug-related, medical, psychiatric and social). It is also important to explore the patient's goals and expectations as part of the engagement process.

SIDE-EFFECTS OF OST

Side-effects due to OST are common during treatment initiation after which tolerance develops for many. Some early side-effects of OST may be difficult to differentiate from withdrawal symptoms (nausea, joint aches, sweating, insomnia [buprenorphine – headache, hyperactivity]). Some side-effects are chronic problems, particularly constipation, sweating, sleep disturbance, endocrine changes (reduced libido, amenorrhoea) and dental problems.

The successful management of these side-effects during maintenance OST can have a dramatic impact on adherence to the programme.

METHADONE SUBSTITUTION THERAPY

In particular, methadone has potential benefits in resource-constrained settings because of its remarkable effectiveness, the stabilizing effect of daily dosing, its effectiveness in reducing criminal activity and drug use, effectiveness in relieving chronic pain, safety in pregnancy, low cost (average doses less than US\$ 0.25 per day (<US\$ 0.5 per mg)) and its low diversion potential with observed dosing.

Despite its effectiveness, buprenorphine is less satisfactory in this setting because of its high cost and higher diversion potential.

OST IN ASIA

Currently, OST with methadone has been long established in Hong Kong with less satisfactory programmes in Thailand and Nepal. New initiatives include scaling up OST with methadone in China, Myanmar, Indonesia and Malaysia and OST with buprenorphine in India and Pakistan. Buprenorphine use for opioid detoxification in Indonesia, Malaysia and China is widespread and poorly controlled.

OST with methadone is an extraordinarily cost-effective treatment that is in keeping with the Asian values of family, employment and social inclusion. Currently, it receives WHO and UNODC support for its inclusion in National Essential Medicines lists and the large-scale expansion of access to treatment programmes.

SUMMARY

To successfully manage opioid dependence, it is necessary to:

- Understand and recognize the features of opioid dependence and withdrawal syndromes
- Carefully evaluate clients for treatment
- Safely commence withdrawal or maintenance treatment
- Understand the basic components of OST

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Mattick RP et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Systemic Review*, 2003, (2): CD002207. Update in: *Cochrane Systemic Review*, 2004, (3): CD002207.

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EXERCISE 4.2.1

CASE STUDY

Please read the following case study.

Budi is a 28-year-old casually employed man who lives with friends in an inner city share house. He comes to the doctor to join an opioid substitution programme.

History:

Heroin: started heroin use at age 17, injecting, dabbled for several months, regular use since age 19, most friends were using heroin at the time, one was “dealing”, started using daily.

Past twelve months, daily use three times per day (usually US\$ 10–20)

Other drugs:

Cigarettes – daily since age 15, 20/day

Cannabis – regular, 2–3 nights/week, 2–3 joints

Benzodiazepines – occasionally for detox, none for 3/12

Alcohol – none

Attempts to stop: withdrawals ++ at home and with outpatient medication

Risks:

Never overdosed

Shared injecting equipment with previous friends

Worried about bloodborne virus infections, particularly HIV

Medical history:

Past hepatitis B (not a carrier)

Psychiatric history – none relevant

Social history – living with friend in a share house, two friends are using but trying to stop too

Currently single

Goals: wants to stop using, has thought about methadone

Physical exam:

Injection marks in both cubital fossae, evidence of recent and long-term use

Thin and ill-kempt

Small group discussions:

Break up into small groups to discuss these questions. Choose a speaker from your group who will report back to the class. Spend about 5–10 minutes to discuss the following question:

1. What are your concerns and how do you advise Budi?

EXERCISE 4.2.2

ROLE-PLAY: AHMED

Instructions for role-play:

- Break up into groups of three: one doctor, one patient and one observer.
- Only the patient has access to the case notes.
- Conduct a history-taking assessment – there may be some signs – so ask!
- Spend 15 minutes on each interview. Then we will discuss the assessment and clinical management plan in the large group.

Role-play: patient

- You are to read and try to reproduce the client's degree of neuroadaptation, dependence and risk
 - You can ask if methadone treatment is appropriate
 - You should be insistent if the doctor does not agree
- You should be asked about features in the client's presentation that warrant a low initial dose
 - You should negotiate a starting dose
 - You can make it known if you are not comfortable with this choice
- You can ask to have the induction process explained
 - Did the doctor explain methadone well:
 - The cumulative effect of methadone?
 - The overdose risks associated with other drug use and the importance of reporting any continued drug use?
- Are there any problems with such an interview in "real life"?

Role-play: doctor

- What is your assessment of the client's degree of:
 - Neuroadaptation? dependence/risk?
- Is methadone treatment appropriate?
- Are there any features in the client's presentation that warrant a low initial dose?
 - What starting dose was negotiated?
 - Was the client comfortable with this choice?
- Did the client understand the induction process?
 - The cumulative effect of methadone?
 - The overdose risks associated with other drug use and the importance of reporting any continued drug use?

Role-play: observer

- What is your assessment of the client's degree of:
 - Neuroadaptation? dependence/risk?
 - Is methadone treatment appropriate?
- Are there any features in the client's presentation that warrant a low initial dose?
 - What was the starting dose negotiated?
 - Was the client comfortable with this choice?
- Did the client understand the induction process?
 - The cumulative effect of methadone?
 - The overdose risks associated with other drug use and the importance of reporting any continued drug use?
- Are there any problems with such an interview in "real life"?

Role-play

Ahmed is a 25-year-old printer who lives with his parents. He comes to the doctor to get on an opioid substitution programme.

History:

Heroin: heroin use since age 19, now using ½ g daily, injects 1–2 times per day. Last used yesterday.

All his money goes in buying drugs.

Other drugs:

Uses benzodiazepines in binges when he can get them from a friend. Usually 5–6 oxazepam or diazepam once per fortnight after dancing all night at a party
Has 1 or 2 glasses of beer, not more.
Sometimes uses Ecstasy at a party.

Attempts to stop: now gets withdrawal effects from heroin. Multiple detox attempts at home.

Risks: Had one previous heroin overdose two years ago

Social history: Girlfriend smokes a little cannabis, occasionally uses Ecstasy, but no intravenous (IV) drugs

Goals: Never been on methadone before, but some of his friends are on methadone and he tried some of their take-away doses and found it acceptable.

Physical exam:

Fit-looking young man
Pupils slightly dilated
IV injection track marks in left cubital fossa

Features of a comprehensive OST programme

OVERVIEW



Objectives:

By the end of the session the participants will be able:

- To understand the features of an opioid substitution programme and the requirements for additional interventions
- To assess the indications for opioid substitution withdrawal and the support required
- To assess clients for counselling and referral to other treatment and assistance modalities



Time to complete session:

1 hour 45 minutes



Session content:

- Ceasing OST
- Impact of maintenance opioid withdrawal
- Extra requirements of injecting drug users on ART
- Post-withdrawal interventions
- Summary



Training materials:

- PowerPoint presentation 4.3: Managing opioid dependence: features of a comprehensive OST programme
- Sub-module 4.3: Features of a comprehensive OST programme
- Annex 1: Pharmacodynamics of opioids
- Exercise 4.3: Case studies

CEASING OST

When and how to stop OST is probably the most uninvestigated and poorly taught component of OST programmes, but in general the longer patients remain in treatment the better their outcomes. This is probably because there is a high relapse rate to dependent heroin use for patients who prematurely stop methadone or who have not stopped heroin use for a substantial amount of time when they try to stop methadone.

So when is it time to stop? Any assessment for this must take into account the patient's behavioural factors such as cessation of heroin use, existence of social stability with good supports and relationships, and the presence of treatment-related factors such as stability of dose, good treatment adherence and good clinic relationships.

Despite the implementation of these assessment factors, it is not possible, however, to keep patients involuntarily in methadone or buprenorphine treatment. Most patients will experience frustration with the OST programme at some stage and attempt at least one premature reduction in maintenance opioids.

Patient factors of particular relevance

It is recommended that before starting OST reduction the patient should be free of all heroin intake for more than six months and have the triad of stable social supports – stable employment, stable accommodation and a stable, supportive, intimate relationship.

It is important that these be seen as markers of recovery rather than a list of things "to do". Hence, the answer to one of the most commonly asked questions in OST – "when can I stop the treatment?" – is to be answered as, "when you are well on the way to recovery" (as assessed by these psychosocial measures).

IMPACT OF MAINTENANCE OPIOID WITHDRAWAL

The impact of methadone or buprenorphine dose reduction is to not experience "opiate withdrawal symptoms" unless the dose is decreased too rapidly. Instead, the patient is likely to experience a dysphoria similar to the premenstrual syndrome with unstable emotions, irritability, aggression and anger, with low frustration tolerance and a lack of insight. The presenting symptoms are often articulated as "not coping".

Methadone reduction

To avoid losing the gains made in recovery, it is necessary to decrease OST very gradually. With methadone this should generally be no faster than 5 mg/month with a recommended maximum decrease of 10% of the daily dose each fortnight. From experience, the most effective regimen is to reduce by 1 mg per fortnight *with occasional respite* and to watch for dysphoria, which may be greatest as the dose approaches zero.

Many patients reach a dose level (often between 10 and 30 mg) at which dysphoria or discomfort increases and if heroin use is resumed, restabilization will then be required on a higher dose.

A reduction in the daily dose of 25 mg per year is achievable for most people if their stability factors are maintained, with even faster reductions possible if the patient relocates to a new area.

Buprenorphine reduction

Following the themes outlined above, gradual reduction of buprenorphine is still recommended. Because it is associated with fewer withdrawal symptoms, buprenorphine reduction is often undertaken prematurely and far too rapidly.

In making the decision to reduce OST, the fundamental understanding of the neurobiological changes in the brain requires reinforcement. With a reduction in the dose of buprenorphine, opioid withdrawal symptoms are very rare, but the rule of thumb is that reduction of the daily dose should proceed no faster than 2 mg/month, and with a recommended maximum of 10% of the dose each fortnight (even as small 0.1–0.2 mg). Relapse to heroin use can be subtle and unexpected with many patients requesting a change to OST using methadone after a number of failed reduction attempts on buprenorphine.

Contraindications to OST withdrawal

There are a number of physical, social and behavioural contraindications to OST withdrawal with a variety of expected adverse outcomes if withdrawal is not avoided. The most obvious is ongoing heroin use, with a predictable deterioration in drug consumption and lifestyle control in the presence of decreasing opioid support. There are severe adverse outcomes for the fetus in the presence of a pregnancy with the possible outcomes of spontaneous abortion, intrauterine fetal death, premature labour and stillbirth if opioid withdrawal is forced. In the presence of pain or depression, a deterioration in the symptoms of both can be expected with OST reduction.

The other group of contraindications are of a social nature with looming critical events such as school or university examinations, new employment, a new relationship or unstable other drug use. All are likely to be disrupted by the dysphoria of opioid withdrawal. If possible, in the presence of such unstable social factors, OST reduction should be postponed until recovery has reached a more stable and resilient stage.

Sudden methadone cessation

Opioid withdrawal is never lethal unless caused by naltrexone administration: however, the sudden stoppage of methadone OST is to be avoided at all costs because of the destabilizing and protracted nature of the withdrawal experience, which typically lasts six weeks and may last up to twelve weeks.

With methadone cessation withdrawal symptoms start after two or three days and peak in the second and third week with insomnia, restlessness and difficulty in getting comfortable, back pain, severe dysphoria (“something missing”), irritability and depression. Rarely, a schizophreniform psychosis may be seen.

EXTRA REQUIREMENTS OF INJECTING DRUG USERS ON ART

In the presence of HIV disease there exists the opportunity for synergies of care for injecting drug users (IDUs) on OST. Typically, higher doses of methadone will be required, and there are advantages if ART services could provide OST.

Although IDUs can, with adequate support, achieve excellent ART adherence, there is documented improved compliance and convenience if OST and ART services are provided together. Extensive research has been conducted on ARV interactions with OST and illicit drugs, and most national ART guidelines include provision of OST and training of health-care providers in combination HIV care with ART, OST and TB treatment.

In addition, the provision of comprehensive care programmes for IDUs including OST, ART and appropriately targeted peer interventions and behaviour change communication (BCC) materials makes logistic sense in most countries in this region because the target populations for OST and ART are the same.

POST-WITHDRAWAL INTERVENTIONS

Many if not all of the traditional post-withdrawal interventions can be added to a successful OST programme. The most popular interventions are psychosocial interventions using relapse prevention counselling, vocational training, occupational assistance, education, legal advice and self-help groups.

Where appropriate resources are available, higher-level counselling through supportive or narrative therapy, cognitive-behavioural therapy and even psychotherapy can be attractive to some patients.

The addition of family support programmes with family and relationship therapy and family support groups will provide valuable advocacy support for the OST clinic and a useful mechanism for propagating accurate information about OST to the community.

The difficult issue of the provision of residential rehabilitation for drug users in recovery on OST has, despite evidence for the efficacy of the approach, been hampered by the domination of the therapeutic community sector with workers indoctrinated with 12-step abstinence philosophies.

Counselling

The options for counselling in the context of drug dependence are very broad with almost all programmes offering some supportive one-on-one or group counselling. The evidence base for any particular form of counselling over another is not strong and in fact suggests that the relationship with the counsellor and his/her skill is more important than the method or qualifications.

Generic “drug-free” or “drug and alcohol” counselling is associated with reductions in crime and drug use, and is dependent on the quality of the therapeutic relationship. Most studies suggest that high-intensity programmes are best though the drop-out rates are high (perhaps through self-selection).

This type of generic counselling has a lower risk of relapse to drug use over the follow-up period, although this is also influenced by the presence of the characteristics of a good counsellor: strong interpersonal skills, organized in their work, arranges to see patients more frequently (may be a measure of rapport), able to refer patients to other ancillary services, and able to establish and maintain a practical “therapeutic alliance”.

Other types of counselling

Motivational interviewing, which requires specific training and professional distance, depends on the development of cognitive dissonance and has been demonstrated to improve the impact of OST on heroin use. In particular, it has been demonstrated through general practice that brief interventions have an impact on both problematic alcohol and marijuana use.

Motivational interviewing may be helpful for adherence, coupled with assertive outreach and phone or SMS reminders for appointments.

Cognitive-behavioural therapies involve a fixed short programme of planned sessions focusing on relapse prevention. Cognitive-behavioural therapy has demonstrated effectiveness in a number of substance use disorders where the focused series of sessions are planned in advance with exercises and “homework”.

Cognitive-behavioural therapy emphasizes social and communications skills and is important for mood management, stress and in particular for post-traumatic stress disorder.

Multicomponent behavioural counselling is a mixed community reinforcement, contingency contracting and family therapy model that is popular in the USA where intensive programmes with individual design have been found to be more effective than Alcoholics Anonymous (AA) or standard drug counselling.

Self-help groups including Narcotics Anonymous, AA and Rational Recovery (RR) are the franchise face of peer support networks. They meet regularly to provide a safe, drug-free social context and share experiences and recovery stories. It appears that self-selection is all important for effectiveness and that *involvement* (versus just attendance) in weekly meetings appears critical for impact. Note that for unselected referrals these self-help groups offer little advantage over placebo.

Psychiatric care

There is an exceedingly high prevalence of co-morbid mental health problems in drug users, with 40–50% of patients who enter methadone treatment having a diagnosable mental illness. Most commonly, this presents as depression, anxiety, schizophrenia, post-traumatic stress disorder, bipolar disorder or personality disorder. In addition, more than 25% of patients attending mental health services have a substance use disorder.

For this sub-group with co-morbid mental illness, the strategies that seem to assist their care are assertive follow up and formal referral mechanisms for mental health assessments, which are warranted for patients with psychoses, mania, suicidality and personality disorder, even though many of the patient’s symptoms will improve on OST. Many patients on OST will require treatment for depression or of anxiety at some time.

Employment

The role of study or work in recovery cannot be overstated, and a productive place in society is critical for recovery. Occupation assists a recovering drug user to fruitfully utilize time that was otherwise spent in drug-using activities, and provides a supportive co-worker network and a potentially supportive employer. Employment should be pursued to the stage of stability, and ability to tolerate the dysphoria and irritability associated with OST reduction.

The loss of employment is often a prelude to relapse to drug use.

Relationships

The support provided by an intimate relationship is another vital component of the recovery journey. Such relationships are distracting, supporting and nurturing; children are an important component. It is important to nurture these relationships to such a level that patients become stable and able to tolerate the emotional upset of OST reduction. This does not include the unconditional love of a parent.

Relationship breakdown is a common prelude to relapse into drug use.

Accommodation

This is the third vital stability factor in full recovery, and it is important as a component of stable re-entry into society and a measure of reintegration. Neighbours and living companions are an important part of a society's support network and should be nurtured until there is no risk of eviction. It is difficult to reduce OST when living with parents or other relatives.

Homelessness is another important prelude to relapse to drug use.

Peer group support

The slow establishment of a stable non-drug-using network heralds the recovery from dependence. It is very difficult to initiate and the three factors described above often support the development of this network of friends. Sometimes the network can be generated out of good work (in an NGO or community group), while many ex-drug users become involved in helping other users or as peer outreach workers. In many drug treatment agencies there is a slow transition from patient to vital staff member of a health service for a number of drug users. However, the risk of relapse to drug use remains high for many years if a patient continues to work in the drug treatment sector.

Loneliness, boredom and social isolation are powerful triggers for relapse.

Miscellaneous aids to recovery

Many other activities appear to assist some people during their recovery. These include the learning of an alternative recreation, restoration of general health, physique and fitness, investment in dental health, recovery of libido and sexuality, finding of a voice for opinions and communicating with peers, writing, public speaking or research. The (re) discovery of spirituality through religion, meditation, yoga or an appreciation of the environment also seems to be a useful, though sometimes elusive, aid to recovery.

SUMMARY

Additional services are available to support OST withdrawal. It is important to understand and provide some of these additional features of an OST programme and to know when to initiate these interventions. The evaluation of patients for counselling, and referral to other treatment/assistance modalities is an important part of a drug treatment service with or without OST.

EXERCISE 4.3

CASE STUDIES

Case study 1

Please read the following case study.

A 29-year-old woman with a seven-year history of heroin use (IV)

She now uses heroin two–three times per day (US\$ 10) for the past year with no acknowledged benzodiazepine or cannabis use. She has had four previous detoxification attempts (the last was three months ago, which lasted for two days). She has had one previous methadone treatment about one year ago for six months and reached a dose of 50 mg which “helped”, but she became tired of collecting the methadone doses and abruptly discontinued the programme.

She has a post history of an overdose three years ago. She lives alone since her partner (“dealer”) was arrested one month ago. Her last menstrual period was four months ago. She is not working.

She was restarted on an initial methadone dose of 20 mg three days ago. She complains of withdrawal symptoms each night, and that the methadone only “holds” for around eight hours. She denies any heroin use since restarting methadone.

On examination she is a thin woman, injection sites scarred but not infected. There are no features of opiate withdrawal or intoxication.

Her urine result from day 1 reveals:

Opiates and benzodiazepines +++

Pregnancy test negative

She requests a dose increase by 10 mg.

Small group discussions:

Break up into small groups to discuss this question. Choose a speaker from your group who will report back to the class.

1. What are the issues within the OST programme and some of the interventions required?

Case study 2

Please read the following case study.

Ari, 26 years of age, was in your methadone programme (stable daily dose of 85 mg) until six weeks ago, when he suddenly stopped attending.

He had stopped using heroin while on methadone, but went on alcohol binges (bouts of excessive use), often drinking up to four litres of “wine” on a weekend once per month.

He presents again with a request to restart methadone.

On examination, his breath smells of alcohol, he looks pale and sweaty, has a mild tremor and dilated pupils. He has severe epigastric and right upper quadrant abdominal pain and tenderness.

Small group discussions:

Break up into small groups to discuss these questions and try to identify the issues within the OST programme and some of the interventions required.

Choose a speaker from your group who will report back to the class.

1. **What more information do you want (history, exam, investigations)?**
2. **Should a referral be made – where/when?**
3. **What psychosocial interventions could be helpful over time?**

Case study 3

Please read the following case study.

Budi stopped methadone after several days of very heavy use of amphetamines, during which he failed to pick up his methadone. He also owed the dispensary approximately US\$ 25 in fees.

Since stopping methadone, he has been using heroin two to four times every day and drinking up to four bottles of beer some days. He has used benzodiazepines and amphetamines only occasionally, once or twice a week and the last time was two days ago.

You initiate some blood tests when restarting his methadone and the results 48 hours later are:

LFTs: GGT 457; ALT 162; remainder normal

UDS: opiates positive

Full blood examination: normal

Small group discussions:

Break up into small groups to discuss these questions. Choose a speaker for your group who will report back to the class.

1. **What are the issues within the OST programme and some of the interventions required?**
2. **What referrals would you make and with what psychosocial interventions?**

Case study 4

Please read the following case study.

Lia started your OST programme eight days ago.

She complained that the dose was not holding her and you increased it on the third day and then again on the sixth day. She still complains of withdrawal discomfort and is using heroin once a day. She is in financial debt and tearfully tells you how she will be evicted from her flat if she does not pay the rent this week.

In short, she feels that she cannot continue using heroin but she has heard from a friend that OST is “no good in high doses” and is therefore reluctant to increase her dose further.

Small group discussions:

Break up into small groups to discuss these questions. Choose a speaker from your group who will report back to the class.

- 1. What are your thoughts on the management of the OST?**
- 2. Which psychosocial interventions would be helpful?**

Pharmacodynamics of opioids

Adapted from: *Pharmacotherapy training program for opioid dependence*. Victoria, Australia: Department of Human Services, 2004.

In general, opioids decrease the spontaneous activity of neurones, producing drowsiness, mood changes and mental clouding. They are distinguished from the sedative–hypnotics by their powerful analgesic, cough suppressant and antidiarrhoeal properties.

Opioids act on specific receptors in the brain, spinal cord and limbic system. (The limbic system is involved in the sensation of emotions. Some areas produce pleasure when stimulated.) Five families of opioid receptors have been identified; μ (mu) receptors (μ_1 and μ_2), δ (delta) receptors (δ_1 and δ_2), κ (kappa) receptors and the more recently discovered σ (sigma) and ϵ (epsilon) receptors.

All prescription opioids have a major impact on the μ -receptors to produce analgesia and euphoria. There is an associated decrease in respiratory rate, muscle tone, movement in the digestive tract and changes in hormones. The activation of κ -receptors results in analgesia (especially at the spinal cord level) such as sedation, sleep, urine production and miosis. Activation of the δ -receptors impacts on drug reinforcement, respiration and mood, and may contribute to analgesia. Both the μ -receptors and the δ -receptors are associated with dependence. Stimulation of the μ -receptors affects the neurotransmitters dopamine, gamma-aminobutyric acid and serotonin. The ϵ -receptors appear to be involved in modifying nociception.

SHORT-TERM EFFECTS OF OPIOIDS

Table 2. Common opioid effects (e.g. morphine, heroin, methadone)

| | |
|---------------------------------------|--|
| Nervous system | Analgesia Euphoria Sedation, drowsiness Suppression of cough reflex Respiratory depression Pupillary constriction Convulsions (in very high doses, not common) |
| Gastrointestinal tract actions | Nausea and vomiting Reduced gastric emptying, increased pyloric sphincter tone Constipation |
| Endocrine actions | Reduced FSH and LH; elevated prolactin resulting in menstrual changes; galactorrhoea Reduced testosterone in males, with reduced libido and gynaecomastia Elevated antidiuretic hormone (ADH) Reduced adrenal corticotrophic hormone (ACTH) |
| Skin | Itching, sweating, flushed skin from histaminic reaction Dry mouth, skin and eyes |
| Cardiovascular | Orthostatic hypotension |
| Other | Inhibits urinary reflex, difficulty passing urine |

PHARMACOKINETICS OF OPIOIDS

Buprenorphine

Buprenorphine undergoes extensive first-pass metabolism in the liver, and is therefore unsatisfactory for oral use. It is available therefore as a sublingual preparation that takes about 5–15 minutes to dissolve. It is principally metabolized by two hepatic pathways: conjugation with glycuronic acid and N-dealkylation. While current evidence is inconclusive, it is thought that the concurrent use of medications that induce or inhibit microsomal enzyme activity have minimal clinical impact on buprenorphine dosing requirements. The metabolites are excreted in the biliary system, with enterohepatic cycling of buprenorphine and its metabolites. Most of the drug is excreted in the feces (70%) and urine (30%).

Table 3. Pharmacodynamics of buprenorphine (sublingual dose)

| | |
|-----------------------|---|
| Onset of effects | 30–60 minutes |
| Elimination half-life | 24–37 hours |
| Peak clinical effects | 1–4 hours |
| Duration of effects | 8–12 hours at low doses (e.g. <4 mg) 24–72 hours at high doses (e.g. >16 mg) |

The extended duration of action of buprenorphine is thought to relate to two factors: (1) very high affinity for opioid μ -receptors (once bound to these receptors it is dislodged only slowly); and (2) high lipophilicity (low levels of buprenorphine are released slowly from fat stores, particularly with chronic dosing). The prolonged duration of effect at high doses enables alternate-day, and even 3 days-a-week dispensing regimens.

Table 4. Key clinical pharmacological properties of buprenorphine

| Property | Clinical Implication |
|---|---|
| Produces opioid effects | Reduces craving for heroin and enhances treatment retention Less sedating than full agonists (heroin or methadone) |
| Prevents or alleviates heroin withdrawal symptoms | Can be used for maintenance or withdrawal treatment |
| Diminishes the effects of additional opioid use (e.g. heroin) | Diminishes psychological reinforcement of continued heroin use May complicate attempts at analgesia with other opioids |
| Long duration of action | Allows for once-a-day to three-times-a-week dosing schedules |
| Ceiling on dose–response effect | Higher doses (e.g. >16 mg) may not increase the opioid agonist effects, while prolonging the duration of action. Safer in overdose, as high doses in isolation rarely result in fatal respiratory depression |
| Sublingual preparation | Safer in accidental overdose as poorly absorbed orally More time involved in supervised dispensing |
| No severe withdrawal precipitated by opioid antagonists | Treatment with naltrexone can be commenced within days of buprenorphine. May complicate management of heroin overdose requiring high naltrexone doses |
| Side-effect profile similar to other opioids | Generally well tolerated, with most side-effects transient. A side-effect of note is the phenomenon of precipitated withdrawal. |

Codeine

Codeine is approximately 60% as effective orally as parenterally. Very few opioids have so high an oral–parenteral potency ratio. Oxycodone and methadone also share this attribute. The greater oral efficacy of these drugs is due to less hepatic first-pass metabolism. Once absorbed, codeine is metabolized by the liver and excreted chiefly in the urine, largely in inactive forms. A small fraction (approximately 10%) of administered codeine is converted to morphine, its active form via demethylation by the enzyme CYP 2D6. This enzyme is absent in about 8–10% of Caucasians and about 2% of South-East Asians. In such individuals codeine has no analgesic effect. Both free and conjugated morphine can be found in the urine after therapeutic doses of codeine. Codeine has an exceptionally low affinity for opioid receptors, and the analgesic effect of codeine is due to its conversion to morphine. However, its antitussive actions probably involve distinct receptors that bind codeine itself.

Methadone

Safe and effective treatment with methadone depends to a large extent on an understanding of the pharmacology of methadone.

The key information regarding the pharmacology of methadone is as follows:

- It is well absorbed orally due to its high bioavailability.
- It has a slow onset of effects – effects commence within 30–60 minutes following ingestion.
- Peak effects are usually 2–4 hours after an oral dose (features of intoxication to methadone will be most evident at this time).
- Steady-state equilibrium achieved after 5 half-lives – approximately 5 days.
- Methadone is stored in fat and in the liver. Therefore, the first dose is significantly sequestered in adipose tissue so blood levels are lower than achieved after the second dose. Thus, clinical effects increase with repeated dosing.
- The half-life of methadone is approximately 12–18 hours after a single dose and 20–24 hours after repeated dosing.
- It is metabolized predominately in the liver to inactive metabolites by the cytochrome p450 system (predominately isoenzyme 3a4).

Approximately 10% of methadone administered orally is eliminated unchanged in the urine (which can be detected by a urinary drug screen). Renal disease appears to have minimal clinical impact.

Factors impacting on metabolism include individual variations in patient response and potential drug interactions and disease states. Due to the significant interpatient variability of the pharmacokinetics and pharmacodynamics of methadone, methadone treatment must be clinically titrated for each patient.

Morphine

When therapeutic concentrations of morphine are present in plasma, about one-third of the drug is protein bound. Morphine itself does not persist in tissues, and 24 hours after the last dose tissue concentrations are low.

Although the primary site of action of morphine is in the CNS, in the adult only small quantities pass the blood–brain barrier. Compared with other more lipid-soluble opioids such as codeine, heroin and methadone, morphine crosses the blood–brain barrier at a slower rate.

The major pathway for the metabolism of morphine is conjugation with glycuronic acid to form both active and inactive products. Morphine-6-glucuronide, a major metabolite of morphine, has pharmacological actions indistinguishable from those of morphine.

Very little morphine is excreted unchanged. It is eliminated by the kidneys primarily as morphine-3-glucuronide; 90% of the total excretion takes place during the first day. Enterohepatic circulation of morphine and its glucuronides occurs, which accounts for its detection in the urine for several days after the last dose.

Naloxone

Naloxone is a pure μ -receptor antagonist. It has no intrinsic activity when it binds to the μ -receptor and antagonizes the effect of opioid agonists due to its high receptor affinity. When naloxone is administered to a patient intoxicated with an opioid agonist, it reverses intoxication and causes a severe precipitated withdrawal syndrome (depending on the dose of antagonist administered). Thus:

- Naloxone is used in emergency situations to reverse the effects of opioid overdose.
- Naloxone challenge test (Narcan test) may be used to establish the presence of opioid neuroadaptation.
- Naloxone may be used in accelerated withdrawal (rapid detoxification).

Naloxone is unsatisfactory for oral administration due to high first-pass metabolism and is thus used either intravenously or intramuscularly. Naloxone has a short half-life (about 45 minutes). The short half-life has important implications in practice. If a patient overdoses on a long half-life drug such as methadone, a single injection of naloxone will rapidly reverse sedation and respiratory depression. However, within about one hour, naloxone will be metabolized, while the long-acting methadone will still be present, and the patient is likely to lapse back into stupor and hypoventilation.

The management of overdose on long-acting opioids is inpatient admission, observation, airways support and multiple bolus doses of naloxone or naloxone infusion. Patients must be observed for a sufficient duration to ensure that the risk of respiratory depression is over before the patient is discharged. In the case of an overdose involving methadone, the patient should possibly be observed for a period of 24 hours and regular naloxone administration should be used to reverse respiratory depression.

Naltrexone

Naltrexone is a pure opioid antagonist at opioid receptors. Significant pharmacological properties of naltrexone include the following:

- A high affinity for opioid receptors and competitively blocks or reverses the effects of other full opioid agonists, such as methadone, heroin and to a lesser extent partial opioid agonists such as buprenorphine
- No positive opioid-like effects (except for pupillary constriction by an unknown mechanism)
- Does not produce physiological tolerance or dependence
- Does not block the effects of any other class of drugs
- No withdrawal syndrome associated with its cessation

Table 5. Pharmacological properties of naltrexone

| | |
|-----------------------------|--|
| Peak clinical effects: | 1 hour |
| Duration of effect: | 50 mg of naltrexone – 24 hours blockage of 25 mg IV heroin 100 mg of naltrexone – 48–72 hours blockage of 25 mg IV heroin |
| Mean elimination half-life: | 4 hours |

Heroin

Heroin (diacetylmorphine) is rapidly hydrolysed to 6-monoacetylmorphine (6-MAM), which, in turn, is hydrolysed to morphine. Both heroin and 6-MAM are more lipid soluble than morphine and enter the brain more readily, producing increased opioid activity and higher abuse potential. Current evidence suggests that morphine and 6-MAM are responsible for the pharmacological actions of heroin. Heroin is mainly excreted in the urine, largely as free and conjugated morphine. 6-MAM is only seen after heroin use, no other opioid metabolism will produce this metabolite. Presence of 6-MAM is therefore diagnostic of heroin use. However, 6-MAM is only seen for several hours after heroin use.

Presentation 4.1: Opioid use, opioid dependence and withdrawal syndromes

Managing opioid dependence

Opioid use, opioid dependence and withdrawal syndromes

Session objectives

- Understand the social, psychological and biological reasons for drug use
- Describe the features of drug use and understand the particular features of opioids and the neurobiology of their use
- Recognize the difference between use and dependence
- Understand “harms” related to drug use
- Understand and recognize the features of opioid dependence and withdrawal syndromes

Focus on drug dependence

- Please write a short description of the last drug-dependent patient you have seen
- Bullet points are fine but note as much descriptive, social context and drug use data as possible
- This may also be reviewed later in the day

Drug use in society – 1

- Exercise – why do we use recreational drugs?
- Try to remember why you started:
 - ◆ Smoking/drinking coffee/alcohol

Drug use in society – 2

- Exercise – why do we use recreational drugs?
- Remember why you started:
 - ◆ Smoking/drinking coffee/alcohol
 - Peer pressure
 - Desire to be mature/role-modeling
 - “Normal” culture/social activity
 - Stress/anxiety/self-medication
 - Advertisements/movies
 - Experimentation
 - Other reasons

Drug use in society – 3

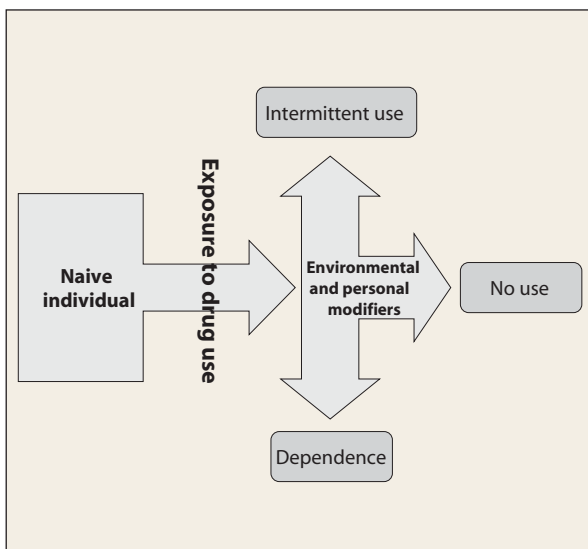
- Exercise – why do we use recreational drugs?
- Now try to think of the reasons you still:
 - ◆ Smoke/drink coffee/alcohol

Drug use in society – 4

- The reasons you still:
 - ◆ Smoke/drink coffee/alcohol
 - Peer pressure
 - "Habit"
 - Stimulation/relaxation
 - Avoid withdrawal
 - Craving
 - Social enjoyment/inclusion
 - "To take a break"
 - Unable to stop
 - Other reasons

Drug "use" versus "dependence"

- Clearly most drugs are used rather than abused:
USE > **Problematic use ("ABUSE")**
USE > **DEPENDENCE**
USE > **Problematic use ("ABUSE")**
USE
- **Rate of dependence among "users":**
 - Nicotine >30%
 - Heroin 25%
 - Cocaine >15%
 - Alcohol 10–15%
 - Cannabis <5% (controversial)
 - ATS ???



Dependence is a typical chronic "health impairment"

- Drug dependence is a chronic, relapsing condition characterized by exacerbation and remission with a number of predisposing conditions and a cycle of evolution and resolution.
- "Life cycle" appears to be predetermined by the drug itself:
 Examples : heroin 10–15 years
 amphetamines 5 years
 cigarettes >40 years
- Relapse is closely related to geographical and social cues

ICD-10 diagnostic guidelines – WHO

A definite diagnosis of dependence syndrome should usually be made only if three or more of the following have been present together at some time during the previous year:

- Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses
- A physiological withdrawal state when substance use has ceased or reduced, as evidenced by:
 - ◆ The characteristic withdrawal syndrome for the substance
 - ◆ Or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms

ICD-10 diagnostic guidelines (cont.)

- **A strong desire or sense of compulsion to take the substance**
- **Difficulties in controlling substance-taking behaviour in terms of its onset, termination or levels of use**
- **Progressive neglect of alternative pleasures or interests because of psychoactive substance use:**
 - ◆ Increased amount of time necessary to obtain or take the substance or to recover from its effects
- **Persisting with substance use despite clear evidence of overtly harmful consequences:**
 - ◆ Including depressive mood states consequent to periods of heavy substance use or drug-related impairment of cognitive functioning

Case studies

- Please discuss these cases in groups of two or three for about 15 minutes:
 - ◆ Suggest alternate groups start with different cases then move on to the other one if time allows
 - ◆ Identify the features of drug use
 - ◆ Identify the characteristic features of dependence
 - ◆ Give feedback to the group on your insights
- What are the characteristic features of opioid dependence?
- What are the possible harms?

Activity 1: small group discussion

Case Study 1: Tan

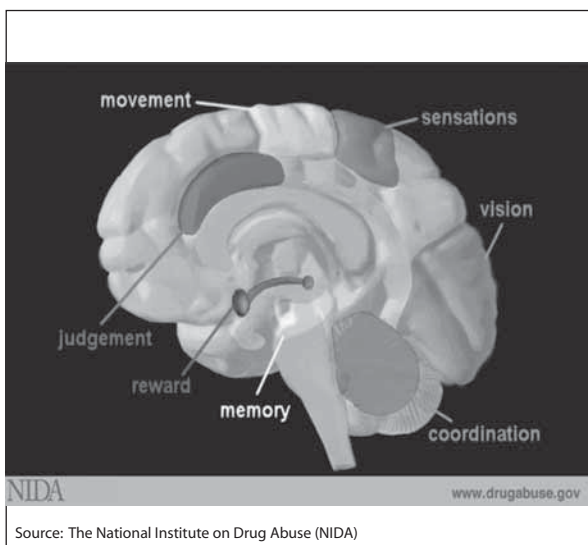
Case Study 2: Ruli

Review Tan and Ruli

- Tan
 - ◆ Withdrawal
 - ◆ Difficulty controlling level of use
 - ◆ Tolerance
 - ◆ Compulsion to use
- Ruli
 - ◆ Withdrawal
 - ◆ Tolerance
 - ◆ Continued use despite problems (financial, infection)
 - ◆ Difficulty controlling level of use

“Natural history” of heroin dependence

- Chronic, relapsing – remitting condition
- Dependence usually starts several years after first heroin use
- There is 2–5% spontaneous remission rate per annum
- There is usually 1–2% mortality rate per annum
- The 10-year outcomes (US treatment seekers) are:
 - ◆ 50% still using and/or imprisoned
 - ◆ 30% abstinent
 - ◆ 20% dead
- Most people stop heroin use by their mid-30s to 40s

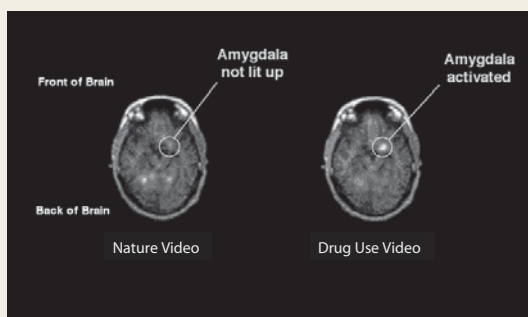


Tolerance and withdrawal = “neuroadaptation”

- Repeated administration leads to:
 - ◆ Decrease in drug receptor density
 - ◆ Change in receptor morphology
 - ◆ Drug receptor desensitization

Cue exposure (after one year drug free)

The memory of drugs



Source: NIDA website. Photo courtesy Anna Rose Childrens.

Activity 2 : heroin-related harms

- In small groups of three or four list the potential harms associated with heroin use:
 - ◆ Spend ten minutes brainstorming together
 - ◆ Then give feedback to a plenary
 - ◆ Perhaps there will be some time to discuss causes of harms and actions to mitigate them
- May be helpful to break them down into:
 - ◆ Biological harms
 - ◆ Psychological harms
 - ◆ Social harms
 - ◆ Economic harms

Switching to injecting drug use



Photo: J. Dorabjee

- Typically (but not always) starts with richer groups and shifts to poorer sectors
- A behaviour change associated with mobility and drug transit routes
- Usually associated with rapid social and economic change



Photo: Peter Higgs

Drug-related harms

Harms associated with injection use:

- Infection
 - ◆ Blood-borne from shared equipment – hepatitis, HIV, malaria
 - ◆ Systemic infections – endocarditis, fungal abscess, osteomyelitis
 - ◆ Local from poor hygiene
- Opioid overdose/death
- Crime/theft/imprisonment/drug syndicates
- Suicide/accidental death/murder
- Sex work
- Financial/poverty/community/legal/stigma

“Reduction of harm”

- Aims to reduce drug-related harm to the individual and the community
- Hierarchy of goals:
 - ◆ “Cure” (abstinence) is ideal
 - ◆ Reducing levels of drug use
 - ◆ Changing high-risk behaviors
- Common paradigm for medicine
 - ◆ Cigarettes/asthma
 - ◆ Obesity/diabetes
 - ◆ Obesity/hypercholesterolaemia
 - ◆ Adolescent risk behaviours

Summary

- Drug use has a long history in Asia.
- Most drug use does not lead to dependence.
- Drug dependence is a chronic relapsing syndrome.
- There are social, psychological and biological reasons for drug use.
- The harms associated with drug use are not in the main related to the drugs themselves.

Drug use and dependence

Summary:

- Understanding of the social, psychological and biological reasons for drug use
- Awareness of the features of opioid use and dependence
- Awareness of the harms of heroin use

Presentation 4.2: Evaluation and treatment of opioid dependence and withdrawal syndromes including OST

Managing opioid dependence

Evaluation and treatment of opioid dependence and withdrawal syndromes including OST

Session objectives

- Understand and recognize the features of opioid intoxication and withdrawal syndromes
- Evaluate clients for treatment and commence withdrawal or maintenance treatment
- Understand the basic components of successful opioid substitution treatment (OST)

Activity 1: heroin effects

Large group discussion

List common physiological effects of heroin/opiate use:

- Brainstorm — think of your own practice with therapeutic opiates (morphine/pethidine/Fentanyl®)

Activity 1: heroin effects

The common physiological effects of heroin / opiate use:

- | | | |
|------------------|---------------------------|--------------------------|
| • CNS | • Analgesia | • Sedation |
| | • Euphoria | • Pupillary constriction |
| | • Respiratory depression | • Coma/death |
| • GIT | • Nausea & vomiting | • Constipation |
| • Endocrine | • Reduced FSH/LH | • Amenorrhoea |
| • Skin | • Itching, sweating, rash | • Histamine rash |
| • Urinary | • Dry mouth and skin | |
| • Cardiovascular | • Urinary retention | • Bradycardia |
| | • Orthostatic hypotension | |

Activity 1: opiate withdrawal

List common features of heroin withdrawal

- ◆ Hint: opposite of therapeutic effects

Discuss the time course of withdrawal

Activity 1: opiate withdrawal

The common features of heroin withdrawal:

- | | | |
|------------------|-----------------------|-----------------------------------|
| • CNS | • Pain and cramps | • Insomnia |
| | • Dysphoria | • Pupillary dilation |
| | • Restlessness | • Anxiety & irritability |
| | • Craving opioids | • Yawning |
| | • Nausea and vomiting | |
| • GIT | • Increased libido | • Diarrhoea/cramps |
| • Endocrine | • Sweating | |
| • Skin | • Rhinorrhoea | • Hair standing up (piloerection) |
| | • Lacrimation | Tachycardia |
| • Cardiovascular | • Hypertension | |

Working with drug users

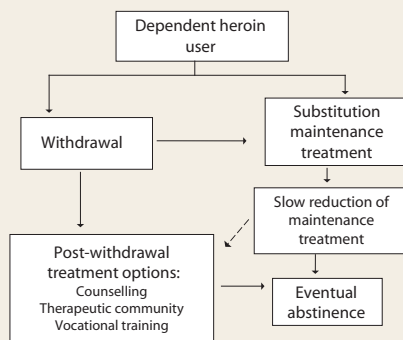
What works — engagement:

- Confidentiality
- Empathy
- Non-judgemental approach
- Accept patient's autonomy to make decisions
 - ◆ (Both good and bad ones)
 - ◆ Adult learning principle – by our experience and mistakes
- Work with the patient to achieve outcomes
 - ◆ “How can you help the patient achieve his/her goals”?

Opiate treatment cascade

- Attempted cessation of drug use
 - Counselling
 - Medicated detoxification/withdrawal
 - ◆ Outpatient
 - ◆ Home
 - ◆ Inpatient
 - +/- naltrexone
 - +/- residential rehabilitation
 - [Prison]
 - Maintenance pharmacotherapies
 - ◆ Methadone/buprenorphine/LAAM
 - “Geographical”
- ↑
Risk of relapse

Treatment pathways for dependent heroin users



Source: Adapted from the *Methadone Training Workshop for medical practitioners*. Royal Australian College of General Practitioners, Turning Point Alcohol and Drug Centre and Monash University Dept. Community Medicine; funded by the Victorian Department of Human Services, Victoria, Australia. www.pac.med.usyd.edu.au/newpac/about.html

Objectives of withdrawal services

Short-term intervention that aims to:

- Alleviate withdrawal discomfort
- Prevent complications of self-managed withdrawal:
 - ◆ Destabilizing medical/psychiatric conditions
 - ◆ Overdose
 - ◆ Social crises
- Interrupt a pattern of heavy and regular drug use
- Facilitate post-withdrawal treatment linkages

Note: Withdrawal is not a “cure” for heroin dependence.

Components of withdrawal services

- Assessment
- Supportive care
 - ◆ Supportive counselling
 - ◆ Safe environment
 - ◆ Provision of information
- Monitoring
- Medications
- Post-withdrawal linkages

Medications in opioid withdrawal

- Three broad groups:
 - ◆ Opioid substitutes controlled and weaned over a short period
 - Methadone, buprenorphine, codeine, opium, dextropropoxyphene
 - ◆ Symptomatic treatment
 - Clonidine, benzodiazepines, loperamide, NSAIDs
 - ◆ Controversial accelerated withdrawal using opioid antagonists
 - Naltrexone/naloxone/deep sedation (benzodiazepines)
- All withdrawal treatments are for symptomatic relief
 - ◆ None have been shown to have good long-term outcomes
 - ◆ Some are associated with treatment mortality
 - ◆ All are associated with increased post-withdrawal mortality
 - ◆ Opioid medications have highest completion rates and best symptom control:
 - Methadone ≥ buprenorphine > codeine or opium tincture
 - ◆ Need great care with outpatient benzodiazepines and opiates

Post-withdrawal interventions

- Counselling
 - ◆ Various models (supportive, behavioural, cognitive, dynamic)
- Residential rehabilitation/TC
- Self-help (Narcotics Anonymous)
- Naltrexone
 - ◆ Opioid antagonist that reduces cravings and blocks effects of additional heroin use
 - ◆ Daily dosing
 - ◆ Effective for those who take it, but extremely high dropout rate
- Non drug-related services
 - ◆ Employment/vocational training
 - ◆ Education
 - ◆ Socialization outside of previous drug culture

Objectives of substitution maintenance treatment

- To reduce heroin and other drug use
- To reduce mortality
- To reduce transmission of bloodborne viruses
- To improve the patient’s general health and well-being (psychosocial functioning)
- To reduce drug-related crime

Overview of substitution maintenance treatment

- Provision of a long-acting opioid (e.g. methadone, buprenorphine):
 - ◆ Enables the patient to cease or reduce their heroin use and related harmful behaviours
- Long-term treatment approach (number of years):
 - ◆ Provides opportunity for patients to distance themselves from drug-using lifestyle and re-enter “normal” society
 - ◆ Controls drug craving and opioid use allowing slow neurobiological recovery to occur
- Combines medication with psychosocial services
 - ◆ Repair the damage to psychology and socialization caused by years of illicit drug use

Comparing treatments for opioid dependence – summary

| Intervention | Effects on heroin use, retention at one year | Mortality | Goal |
|----------------------------|---|-----------------------|--|
| None | 5 – 10% long-term abstinence | ~2%/year | “Drug free” |
| Withdrawal | < 5% long-term abstinence | ~2%/year 1 after. | “Drug free” |
| Methadone Maintenance | 50% retention @1 year 25% no heroin use @ 1year | 4 – 10 fold reduction | Rehabilitation and long-term retention |
| Naltrexone Maintenance | < 20% retention 6/12 Most “drop-outs” relapse before 1 year | ~2%/year or more | “Drug free” |
| Residential Rehabilitation | Progressive dropout ++, motivation assoc. with external pressure. <15% still in treatment. Highly selected. | Unknown but may ↑ | Rehabilitation and “drug free” |

Activity 2: case study

- **Use Exercise 4.2.1 – Case Study: Budi**
- **Please discuss this case in groups of 2 or 3**
 - ◆ Identify if opioid dependence exists
 - ◆ Discuss previous treatment outcomes
 - ◆ Identify special concerns
 - ◆ Propose treatment recommendations
 - **Spend a total of 5–10 minutes**

Opioid substitution therapy

- Oral methadone liquid
- Sublingual buprenorphine tablets
- Cardiac-related AEs – advise against using levo-alpha-acetylmethadol (LAAM) liquid



Methadone effectiveness

- DASA (NYC 1991) MMT reduces:
 - ◆ Property theft 64%
 - ◆ Overall arrests 54%
 - ◆ Emergency room visits 65%
 - ◆ Psychiatric hospitalization 55%
- Cochrane Review 2003 (Mattick et al.) 13 randomized controlled studies: methadone versus buprenorphine — conclusions:
 - ◆ Similarly effective in treating heroin dependence
 - ◆ Methadone significantly more effective in suppression of heroin use (specifically in high dose)
 - ◆ Methadone significantly more effective in retention of patients in programme

Methadone cost-effectiveness

- NTORS study UK (National Treatment Outcome Study):
For every dollar invested in treatment, there is a return of 3 dollars because of lesser costs of the justice department
- International consensus that MMT saves the community between *7 and 10 times* the programme cost incurred on:
 - ◆ Legal
 - ◆ Law enforcement/incarceration
 - ◆ Health
 - ◆ Social
 - ◆ Insurance
 - ◆ Customs
 - ◆ Deaths

Eligibility for opioid substitution treatment

- Opioid dependent
- Informed consent
- Inclusion criteria (suggested):
 - ◆ Injecting opioids
 - ◆ More than six months dependent use
 - ◆ At least one withdrawal attempt
 - ◆ Able to travel to dispensing site
- Exclusion criteria:
 - ◆ Not wanting maintenance treatment

Methadone pharmacology

- Well absorbed orally. Time course of effects:
 - ◆ Onset 30–60 minutes
 - ◆ Peak 2–4 hours after dose
 - ◆ Therapeutic effects for 15–30 hours (dose related)
- Half-life = 20–24 hours
- Steady state equilibrium only after 5 half-lives = 5 days
- Metabolized by hepatic cytochrome P450
 - ◆ Impacted by drug interactions, individual variation, disease states
 - ◆ Particular interactions with ART and TB drugs

Buprenorphine pharmacology

- Poorly absorbed orally. Taken as sublingual preparation. Time course of effects:
 - ◆ Onset 15–30 minutes
 - ◆ Peak 1–4 hours after dose
 - ◆ Therapeutic effects for 8–72 hours (dose related)
- Half-life = 12–36 hours (dose related)
- Steady state equilibrium only after 5 half-lives = 3–5 days
- Partial opiate antagonist
- Metabolized by hepatic enzymes and conjugation
 - ◆ Little impact by drug interactions, individual variation, or disease states

Initiating methadone

- Start with low methadone doses
 - ◆ According to neuroadaptation:
(Low 15–20 mg/medium 20–25 mg/high 25–30 mg)
- Review the patient frequently
- Titrate the dose carefully to 60–120 mg

“Start low, go slow, aim high.”

Initiating buprenorphine

- Start with low buprenorphine doses
 - ◆ According to recent opiate use
 - ◆ Usually 4–6 mg to avoid precipitated withdrawal
- Review the patient frequently
- Titrate the dose carefully and quickly to 12–20 mg

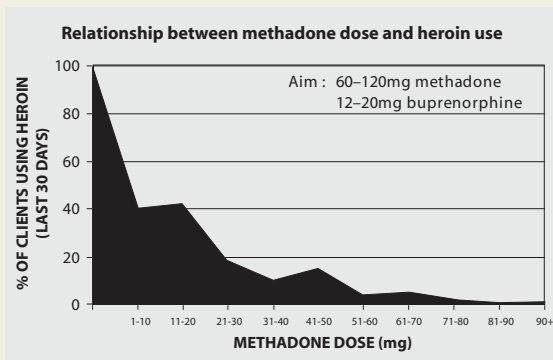
“Start low, go fast, aim high.”

Titration doses

- Increase dose after 3–5 days methadone (steady state)
 - ◆ More rapid dose increases can result in accumulation and toxicity
 - ◆ After 6–8 hours buprenorphine
- Methadone increases of 5–10 mg may be safe if still clearly undermedicated:
 - ◆ Dose increases of >10 mg at a time not safe
 - ◆ Recommend maximum 30 mg increase in any week
- Buprenorphine increases of 4 mg per day safe
- Only increase dose after reviewing patient and where clinically indicated:
 - ◆ In withdrawal
 - ◆ Still using heroin
 - ◆ Thinking/dreaming of using heroin often
 - ◆ Unable to say no to heroin when offered

Increasing dose required

Reduction of heroin use



Source: Adapted from Ball and Ross, 1991.

Key features of the OST assessment

- To engage the patient in the treatment process
 - ◆ Establishing rapport with the patient
 - ◆ Facilitating treatment plans
- Presenting problem
- Drug use (include all drug classes)
 - ◆ Quantity/frequency/route of administration/duration of use
- Severity of dependence and neuroadaptation
- Risk practices/other conditions impacting upon treatment
 - ◆ Drug-related/medical/psychiatric/social
- Patient goals/expectations
 - ◆ Decision on starting dose

Exercise 4.2.2: role-play

- Use Exercise 4.2.2 – Role-play: Ahmed
 - ◆ Break up into groups of three: one doctor, one patient and one observer
 - ◆ Only the patient has access to case notes
 - ◆ Conduct a history-taking assessment – there may be some signs – so ask!
 - ◆ Spend 15 minutes on each interview then discuss the assessment and clinical management plan in the large group.

OST — side-effects

- Side-effects common during treatment initiation, and then tolerance develops for many
- Some early side-effects can be difficult to differentiate from withdrawal symptoms:
 - ◆ Nausea, joint aches, sweating, poor sleep
 - (Buprenorphine – nausea, insomnia, hyperactivity)
- Some side-effects are chronic problems:
 - ◆ Constipation, sweating, sleep disturbances
 - ◆ Endocrine changes (reduced libido, menstruation)
 - ◆ Dental problems

Methadone substitution therapy

Potential benefits:

- ◆ Remarkable effectiveness
- ◆ Stabilizing effect of daily dosing
- ◆ Reduced crime and drug use
- ◆ Effective in chronic pain
- ◆ Safe in pregnancy
- ◆ Inexpensive doses (< US 0.6cents /mg)
- ◆ Low diversion potential with observed dosing



Source: WHO Indonesia

OST in Asia

- Methadone established in:
 - ◆ Hong Kong, Thailand, Nepal
- Methadone scaling up in:
 - ◆ China, Myanmar, Indonesia, Malaysia
- Buprenorphine substitution in:
 - ◆ India, Malaysia
 - ◆ Detoxification in Indonesia, Malaysia, India, China, (Myanmar)

Extraordinarily cost-effective treatment in keeping with Asian values of family, employment and social inclusion

Managing opioid dependence

Summary:

- Understanding and recognition of the features of opioid dependence and withdrawal syndromes
- Evaluation of clients for treatment and commencement of withdrawal or maintenance treatment
- Understanding of the basic components of OST

Presentation 4.3: Features of a comprehensive opioid treatment programme

Managing opioid dependence

Features of a comprehensive opioid treatment programme

Session objectives

- Understand the additional features of a successful opioid substitution programme and the indications for additional interventions
- Assess the indications for opioid substitution withdrawal and supports required
- Assess clients for counselling and referral to other treatment/assistance modalities

Ceasing opioid substitution treatment

- When to withdraw?
 - ◆ There is a high relapse rate to dependent heroin use for clients who prematurely stop methadone
 - ◆ Client behavioural factors:
 - Heroin abstinence
 - Social stability/supports/relationships
- Treatment-related factors
 - ◆ Stable doses
 - ◆ Not missing doses and good clinic relationships
- Cannot involuntarily keep client in methadone treatment

Client factors recommended before starting reduction

- More than six months heroin free
- Triad of stable social supports:
 - ◆ Employment
 - ◆ Accommodation
 - ◆ Relationship

Maintenance opioid withdrawal impact

- No "opiate withdrawal symptoms" unless decreasing far too fast
- Instead:
 - ◆ Dysphoria similar to pre-menstrual syndrome:
 - Emotional
 - Irritable
 - Aggressive/angry
 - Lacking insight
 - Low frustration tolerance
 - "Not coping"

Methadone reduction

- Gradual reductions recommended
 - ◆ Rule of thumb: no faster than 5 mg/month
 - ◆ Recommended max: 10% of dose each fortnight
 - ◆ Often the most effective regime is 1 mg per fortnight with occasional respite
- Withdrawal may be greatest as dose reaches zero
 - ◆ Many clients reach a dose level (often 10 to 30 mg) at which dysphoria/discomfort increases and heroin use resumes
 - ◆ Restabilization on a higher dose then required
 - ◆ 25 mg per year achievable for most people if stability factors maintained – even more if client relocates to new area

Buprenorphine reduction

- Gradual reductions still recommended
 - ◆ Opioid withdrawal symptoms very rare
 - ◆ Rule of thumb: no faster than 2 mg/month
 - ◆ Recommended max: 10% of dose each fortnight (even 0.2 to 0.4 mg)
 - ◆ Relapse to heroin use subtle and unexpected
 - ◆ Many clients request change to methadone after a number of failed attempts

OST withdrawal contraindications

- Ongoing heroin use
- Pregnancy
- Critical events looming
 - ◆ School/university examinations
- Depression
- New employment
- New relationship
- Pain
- Unstable other drug use

Sudden methadone cessation

To be avoided at all costs!

- ◆ Never lethal unless caused by naltrexone / naloxone administration
- ◆ Withdrawal symptoms start after 2 or 3 days
- ◆ Withdrawal peaks in second and third week
 - Insomnia
 - Restless and difficulty getting comfortable
 - Back pain
 - "Something missing" dysphoria
 - Irritability
 - Schizophreniform psychosis
 - Depression
- ◆ **May last 6–12 weeks !!**

Extra requirements IDUs on ART

- Opportunity for synergies of care
- Higher doses of methadone will be required:
 - ◆ With NVP, EFV, rifampicin, some anticonvulsants
- Oral substitution therapy for IDUs on ART
 - ◆ Improved compliance and convenience
 - ◆ Research on ARV interactions and illicit drugs
- National ART Guidelines include OST
- Training for health-care providers on ART and OST
- Comprehensive care programmes for IDUs include OST
- Treatment literacy about OST tailored for IDUs

Post-withdrawal interventions

- Many if not all traditional interventions can be added to an OST programme
 - ◆ Psychosocial
 - Relapse prevention counselling
 - Psychotherapy
 - Cognitive behavioural therapy
 - Supportive/narrative therapy
 - Family/relationship therapy
 - ◆ Self-help groups
 - ◆ Therapeutic communities/residential rehabilitation
 - ◆ Vocational training/occupational assistance
 - ◆ Education
- Plus the often required legal assistance

Activity 1: case studies

- Use Exercise 4.3 case studies 1, 2 and 3
- Please discuss these cases in small groups then feedback
- Try to identify the issues within the OST programme and some of the psychosocial interventions required

Case study 1: 29-year-old woman

29-year-old woman with seven years of heroin use, using heroin (IV) 2–3 times / day (US\$ 10) for past year; denies benzodiazepine or cannabis use. Had four previous detox attempts (last was three months ago — lasted for two days); one previous methadone episode one year ago for six months, reaching 50 mg — it “helped”, but got tired of picking it up and “jumped off”.

Overdose three years ago. Last menstrual period four months ago. Lives alone since partner (“dealer”) was arrested one month ago. Not working.

Her first methadone restarted dose was 20 mg, three days ago. She complains of experiencing withdrawal symptoms each night and that the methadone only “holds” for around eight hours. She denies any heroin use since starting methadone.

Urine result from day 1 reveals opiates and benzodiazepines ++++. Pregnancy test negative.

There are no features of opiate withdrawal, nor intoxication.

She requests a dose increase by 10 mg.

She is a thin woman; injection sites scarred but not infected.

Case study 2: Ari

Ari, 26 years of age was on your methadone programme (stable dose of 85 mg) until six weeks ago when he stopped attending. He had stopped using heroin while on methadone, but had binges on alcohol — drinking up to four litres of wine on a weekend once per month.

He presents wanting to start methadone again.

Alcohol on breath, looks pale and sweaty, mild tremor and dilated pupils. He has epigastric and right upper quadrant abdominal pain and tenderness.

What more information do you want (history, exam, investigations)?

Should a referral be made — where/when?

What psychosocial interventions could be helpful over time?

Case study 3: Budi

Budi stopped methadone after a “binge” of amphetamine use for several days, during which he failed to pick up methadone. He also owed the dispensary US\$ 25 fees.

Since stopping methadone, he has been using heroin 2–4 hits/day and drinking 2–4 bottles of beer some days. He has used benzodiazepines and amphetamines only occasionally, once or twice a week. The last time was 2 days ago.

Investigation results:

LFTs: GGT 457; ALT 162; remainder normal

UDS: opiates +ve

FBE: normal

What referrals might you make with what psychosocial interventions?

Increased indication for OST

- May require additional supports
- High priority for treatment:
 - ◆ HIV-positive requiring ARV
 - ◆ Pregnant
 - ◆ Requiring DOT for TB
- Increased priority (excellent advocacy potential)
 - Health-care staff
 - Peer workers
 - Important families
 - Highly motivated

OST indication concerns

Precautions:

- ◆ High risk polydrug use
- ◆ Low level neuroadaptation
- ◆ Short duration heroin/opiate use
- ◆ <18 years of age
- ◆ Psychiatric conditions
- ◆ Medical conditions (severe hepatic, respiratory, head injury)
- ◆ Chronic pain
- ◆ Personality disorder (difficult, but has good results)
- Not contraindications, just require a lot of extra care

Activity 2 – case study 4: Lia

Lia started your methadone programme eight days ago on 25 mg. She complained that the dose was not holding her, and you increased it to 30 mg on the third day, and then again to 35 mg on the sixth day.

She now presents complaining of discomfort and is still using heroin once a day. She is in financial debt and tearfully tells how she will be evicted from her flat if she does not pay the rent this week. In short, she feels that she cannot continue using heroin. She has heard from a friend that methadone is “no good in high doses” and therefore is reluctant to increase her dose further.

What would you say to her?

What psychosocial interventions might be helpful?

Activity 2: extra support for Lia

- Increase methadone
 - ◆ Adherence counselling
 - ◆ Understanding methadone doses and effects
 - ◆ Treatment IEC materials
- Social support
 - ◆ Methadone support network
 - ◆ Financial assistance
- Counselling for depression/anxiety
- Medication for depression
- Other underlying concerns

Opioid dependence treatment

Summary:

- Opioid substitution withdrawal indications and supports
- The additional features of an opioid substitution programme and the indications for these additional interventions
- Evaluation of clients for counselling and referral to other treatment/assistance modalities

Treatment and Care for HIV-Positive Injecting Drug Users

The "Treatment and Care for HIV-Positive Injecting Drug Users" training curriculum is designed for clinicians who provide treatment and care, including ART, for HIV-positive injecting drug users. The training curriculum consists of a trainer manual, 12 participant manuals, and a CD-ROM with PowerPoint presentations and reference articles. Topics covered in the curriculum include:

- Module 1: Drug use and HIV in Asia
- Module 2: Comprehensive services for injecting drug users
- Module 3: Initial patient assessment
- Module 4: Managing opioid dependence
- Module 5: Managing non-opioid drug dependence
- Module 6: Managing ART in injecting drug users
- Module 7: Adherence counselling for injecting drug users
- Module 8: Drug interactions
- Module 9: Management of coinfections in HIV-positive injecting drug users
- Module 10: Managing pain in HIV-infected injecting drug users
- Module 11: Psychiatric illness, psychosocial care and sexual health
- Module 12: Continuing medical education
- Trainer manual

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