



SOUTH AFRICAN GUIDELINES FOR THE MANAGEMENT OF OPIOID USE DISORDERS:

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Summary:

Opioid use disorders have disappointing outcomes when treated via conventional methods, including detoxification and rehabilitation. This guideline is an update that is based on current available evidence and consensus of a panel of medical experts in the field of addiction medicine. It aims to provide an overview of the medical treatment of opioid use disorders.

Introduction:

Opioid use disorders are of increasing public health concern worldwide.¹ Severe opioid use disorders are mostly chronic and often life-long conditions that for many patients follow a relapsing and remitting pattern. The aetiology is multifactorial and includes a genetic contribution as well as environmental factors and individual determinants. It is not an illness of “lack of willpower or poor morals”, but rather a complex biological disorder, that is associated with characteristic neurological abnormalities and associated behavioural changes. It is best viewed as a chronic health problem, and is optimally treated via a chronic medical intervention model.²

Heroin is the most commonly abused illicit opioid in South Africa.³ Heroin tends to have salience over other drugs so that individuals who have become dependent on opioids usually prefer it and rarely change their drug of choice. The increased production of opium in Afghanistan has led to increased availability of affordable heroin in South Africa.⁴ Although the fact that South Africa is situated along one of the main drug trafficking routes through Africa explains the increase in heroin use, there is speculation that it may have become a destination in its own right.¹ Heroin is often referred to as “unga” in the Western Cape and can be bought on the streets for as little as R20 to R30 for a “bag”/ “quart”/“beat”/ “hit” or “foil” in Cape Town. Heroin of higher purity, sometimes called “Thai white”, is sold for between R30 and R50 per bag.

“Sugars” is a mixture of cheap heroin and cocaine that can be cut with a variety of other substances that may even include rat poison or other household detergents. It is sold wrapped in plastic in little loops, (often referred to as “loops”) which can cost between R10 and R35, depending on purity. It is popular in Chatsworth, South Durban. There is also increasing use in areas like Kwa-Mashu and Phoenix, North of Durban.

“Nyaope” is a mixture of cheap heroin and cannabis that is commonly used in Gauteng. It is sold cheaply, at about R30 per fix. This mixture is also referred to as “Pinch” in other some areas, like Mpumalanga.

There is debate about the exact content of the street drug, “Woonga”. It is thought to consist of a number of different substances, that may include heroin, crystal methamphetamine as well as rat poison and antiretroviral medications, specifically efavirenz. It is sold most commonly on the streets of Durban for about R20 per hit.

It has also been reported that patients who admit to the use of Cannabis only, subsequently test positive for a variety of drugs, including opiates. There is speculation that other, more addictive drugs, like heroin might be mixed into the cannabis, in order to make patients unwittingly dependent on these drugs.

Furthermore, there has been global concern with regard to the escalating abuse of prescription and over-the-counter opioids. Similar concerns exist within South Africa and there are reports of widespread abuse of especially over-the-counter codeine containing pain medication and cough mixtures, but little data is available with regard to the true extent of this problem.

Epidemiology:

The 2012 World Drug Report estimates that the global annual prevalence of opioid use in 2010 was between 0.6 and 0.8% of the adult population. It estimates that about 19% of injecting drug users were HIV positive while up to 47% were Hepatitis C positive. When looking at Africa, the report warns that experts have noted an increase in heroin use. It estimates that the prevalence for opioid use in 2010 in South Africa was between 0.31 and 0.5% of the adult population.¹

A South African epidemiological study, looking at patients presenting for substance use treatment, found that heroin was the fourth most frequent substance of abuse, with a recorded prevalence of 7.9%.⁵ Furthermore, statistics from the South African Community Epidemiology Network on Drug use (SACENDU) project, a surveillance project looking at substance use trends by gathering data from substance treatment providers since 1996, have shown an increase in heroin use in all sites where data is gathered. More specifically, in Cape Town, in 1997 only 1% of patients sited heroin as their primary drug of abuse; this had increased to 17% by 2011 for the Western Cape. Less than 1% of patients in Durban used heroin as primary substance of abuse in 1996 and by 2011, this had increased to 6.1% for KZN; it had peaked at 31% in 2007, following the “sugars” epidemic in South Durban. Similarly, less than 1% of patients in treatment programs in Gauteng in 1998 used heroin as primary substance, but by 2011, 12.7 % of patients were using heroin as primary drug of choice. In Mpumalanga, less than 1% used heroin as primary drug of abuse in 1999; this had increased to 22.2% in the Northern Region (Mpumalanga and Limpopo) by 2011 (and had peaked at 28.3% in the first half of 2011).³

A higher percentage of females use heroin, (when compared to other drugs, like mandrax and cannabis). Between 8% (central region) and 32% (eastern region) of patients in treatment programs, who used heroin as their primary drug, were females. Of further concern is the high incidence of young patients, who use heroin as drug of choice (up to 17% of those that seek treatment). Furthermore, up to 59% of heroin users are repeat treatment seekers and this underlines the relapsing nature of the disorder.³

In South Africa, heroin is predominantly smoked at present, but the prevalence of injecting use has followed an increasing trend in most regions. There is a misconception that smoking or sniffing heroin is less addictive than injecting use, however many users become heroin dependent in this way. There is wide regional variation in injecting use rates (between 8-18%) and also between racial groups, with the highest rates of injecting use among white patients. The incidence of injecting use is still relatively low compared to many other countries, and this is probably due to a combination of factors, including a significant number of new users who have not progressed to the intravenous route yet, the availability and affordability of

heroin of reasonably good purity and the fact that in many areas, this practice is still relatively uncommon so that many patients have not yet been exposed to this mode of administration. Changes in heroin supply characteristics (e.g. quality or price) may (and in all likelihood will) occur, which may lead to increased rates of injecting use, with associated blood borne infection risk, increased overdose risk and subsequent impact on healthcare.

The true extent of non-medical use of over-the-counter and prescription opioids is unknown. The SASH study, a household survey done in 2002 to 2004, found the prevalence of the use of medications for non-medical reasons, to be 19.3%.⁶ This group includes patients who abuse codeine and other opioid containing analgesic medications and cough mixtures. Up to 11.5% of treatment seekers in substance abuse programs, use over-the-counter/prescription medication as drug of choice and this includes predominantly older females.³ The over-the-counter and prescription opioid patient group is of concern with regard to morbidity in part because of toxicity from other ingredients in many of these preparations, which may include paracetamol and non-steroidal anti-inflammatory drugs.

Neurobiology:

“Opiate” refers to derivatives of opium (such as morphine, diacetylmorphine or “heroin”). “Opioid” refers to all substances, natural and synthetic (such as pethidine), that act on the Mu-opioid receptors in the brain. Routine opiate drug screens test positive only for opiates and special testing is required for synthetic opioids. Mu opioid agonists are primarily responsible for euphoria, sedation and analgesia.

Severe opioid use disorders develop as a result of repeated self-administration of agonists of the mu-opioid receptor (both opiates and synthetic opioids; including heroin, over-the-counter and prescription opioids). With time, profound functional and structural neurobiological changes take place, which affect control of behaviour and motivation, resulting in a chronic relapsing disease. Genetic and environmental factors contribute to the development of this disease.^{7,8} This disorder is associated with distinctive behavioural patterns including compulsive substance seeking and repeated chronic use despite negative consequences even when the user no longer wishes to use and tries hard to stop.⁹ Furthermore, environmental cues become conditioned with opioid reward so that they act as triggers for use, fuelling the repeated compulsion to use. Repeated exposure to exogenous opioids also lead to desensitisation of the opioid receptor; this is associated with tolerance leading to escalating use and with cessation of use, a highly unpleasant withdrawal syndrome. Changes in neuronal composition causes patients to remain at high risk of relapse even after long periods of abstinence.¹⁰ Opioid use disorders therefore usually require long-term treatment as is common with other chronic conditions.

Associated harms:

Opioid use disorders are associated with substantial morbidity and mortality (opioid use increases mortality risk significantly; it has been estimated at between 1-4% per annum¹¹ or up to 15 times compared to general population).¹²

Fatal overdose is a tragic complication, and heroin is often implicated in fatal accidental poisonings. This risk is greatest with loss of tolerance for opioids and with concomitant use of other “downer” drugs, like alcohol or benzodiazepines. Furthermore, it has been hypothesized that an underlying systemic disease (possible a hepatic or pulmonary disorder) may increase an individual’s risk for accidental overdose.¹³ Non-fatal overdoses may lead to neurological

and neurocognitive deficits. Other medical complications arise from non-sterile injecting practices or needle sharing, and include skin or systemic infections, HIV or Hepatitis B or C transmission, and complications because of adulterants, which can include talcum pneumonitis, and renal complications, to mention but a few. Poor general health and heroin's depressant effect on respiration may contribute to lung problems, including pneumonia and tuberculosis. Poly-drug use and the problems associated with these other drugs are also common. Furthermore, heroin use during pregnancy is associated with adverse effects on the pregnancy, including neonatal abstinence syndrome and raises concerns about the parenting ability of mothers with heroin use disorders.

Psychiatric problems among this population are common. Common psychiatric problems include mood disorders, anxiety disorders (including post-traumatic stress disorder), protracted anhedonia (even with long-term abstinence), and personality disorders (especially antisocial and borderline personality disorder). Psychosis is rare but may arise from poly-substance use or other underlying psychopathology.

A study of comorbidity among patients with heroin use disorders at Stikland hospital, Western Cape, provides the only South African data on comorbidity in this population. In the Western Cape, where comorbid methamphetamine use is common (52% of patients), surprisingly high rates of lifetime history of substance-induced psychosis were found (30%). Currently comorbidities included major depressive disorder (26%; more common among females) and anxiety disorders (20%), of which post-traumatic stress disorders were most prevalent (8%). Fifty-nine percent of this cohort met criteria for antisocial personality disorder.

Opioid use disorders are also associated with multiple social harms, including relationship problems, crime, homelessness, burden of social cost due to unemployment, medical and criminal justice costs, family disintegration, impact on family and children, loss of productivity, to name but a few. As many as 83% of participants in the Stikland study had been arrested for drug related crimes and 96% reported family conflict as a consequence of drug use.

Comorbid social, legal, medical and mental health complications require separate identification and appropriate treatment.

Assessment and options with treatment planning:

All patients with non-medical use of opioids require a detailed assessment in order to assess for complications, evaluate for comorbidity, address motivation and treatment goals in order to formulate the most suitable treatment plan.

DSM 5 allows for a diagnosis of an opioid use disorder to be made by looking for evidence of problematic opioid use that lead to impairment and distress in the individual. ¹⁴ It lists eleven possible criteria, of which the user should have at least 2 over a period of 12 months. These include:

1. Taking of opioids longer or in larger amounts than planned
2. Desire or efforts to cut down that are not successful
3. Large amount of time is spent to obtain or use opioids and to recover from its effects.
4. Cravings
5. Role failure in work, school or home as a result of opioid use

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6. Relationship difficulties or social problems due to/or made worse by opioids
7. Important activities are neglected or given up due to opioid use, including at work, social or recreational activities
8. Opioid use is physically hazardous situations
9. Ongoing opioid use even when the individual is aware that it is responsible for, or aggravating medical or psychological problems
10. Tolerance
11. Withdrawal

Patients with 2-3 criteria have mild severity, those with 4-5 symptoms have moderate severity and those with 6 or more symptoms, have severe disorder.

Early identification of the opioid use disorder and early and effective interventions are important. Early detection and treatment usually requires less intense interventions than severe disorders and has better outcomes.

Many treatment ideologies focus on full and total abstinence from all opioids as the only treatment goal. This is not necessary desired by or achievable for all patients. Some may be unable or unwilling to give up all opioids immediately, but reducing illicit opioid use, and engaging patients into a therapeutic relationship can reduce harms. Every assessment should therefore include information on how to reduce harm, including safe sex, prevention of accidental overdose and preventing blood borne virus transmission risk; as well as assessing what the patient hopes to achieve in treatment and their readiness to change.

Realistic goals are important in treatment planning. It has been estimated that heroin addicts use heroin daily for 40-60% of a 20-year addiction career, with both periods of voluntary and involuntary abstinence (e.g. during imprisonment or involuntary treatment).¹⁵

The short-term success rate for total opioid abstinence is thus low, even following inpatient treatment. In a 3-month follow up of 242 opioid-dependent patients in residential treatment in the National Treatment Outcome Research Study 34% of the patients relapsed to heroin use within 3 days, 45% within 7 days, 50% within 14 days, and 60% within 90 days.¹⁶ In the Australian Treatment Outcome Study (ATOS), 92% of patients interviewed at 12 months following detoxification, had used heroin at least once and 15% had overdosed at least once, 89% entered a further treatment episode, with a mean of 3.1 episodes and a mean time of 74 days spent in treatment for the cohort.¹⁵ Total abstinence does however remain an achievable goal for a number of motivated patients and should be attempted if the patient wants it. Short-term abstinence rates may be further improved with the use of an opioid antagonist, like Naltrexone. Abstinence from all opioids with the resultant loss of tolerance does however increase risk for accidental (potentially fatal) overdose and patients should be warned about this.¹³

In view of the poor outcome and potentially increased mortality associated with abstinence-based treatment approaches, most treatment providers have focussed on abstinence from illicit or abused opioids. Many patients want to move away from the drug subculture and stabilise their life, but are unable to sustain total abstinence. In these patients, opioid substitution treatment (OST), using a maintenance dose of a prescribed substitution opioid, should be considered. With OST, most patients either stop illicit opioid use, or only use infrequently, with about only 20-30% reporting ongoing heroin use.¹⁷ OST involves the use of long-term

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oral or sublingual substitute opioids until the patient is ready to change their behaviour and maintain sobriety. It involves substituting in a safe and controlled manner, the illicit or abused opioid that typically has a short half-life and is often smoked or injected, with a long-acting oral opioid agonist or partial agonist, thereby preventing withdrawal symptoms and cravings and providing patients the opportunity to stabilise their lives. Furthermore, in adequate doses using an abused opioid on top, adds no/little extra effect.

The aim of OST treatment is long-term retention in treatment, normalisation of social functioning and reduction of drug-related harm. It has been suggested that it may improve disrupted physiology related to dysphoria frequently seen in abstinent heroin addicts in view of the fact that disrupted cerebral metabolism in methadone maintained patients is less pronounced, especially in areas related to mood, when compared to abstinent heroin users.¹⁸ It is internationally recognised as a safe and effective treatment for this disorder. It has been shown to decrease illicit opiate use¹⁹ and the incidence of high-risk and unlawful behaviours associated with opioid use disorders.²⁰ Oral methadone and buprenorphine are the most widely studied and used agents.²¹

It is encouraging that the proportion of clients, who maintain abstinence from illicit opioids, increases with time and the proportion still addicted, declines. (42% of a cohort of 86 heroin dependent clients, followed up for 33 years, was abstinent from all opioids and had been for at least 10 years; 22% of a cohort had died and death was mostly substance related)²² Over time, most users eventually achieve remission.²³

An ideal service for patients with opioid use disorders should be able to offer an array of treatment options, including opioid free treatment with detoxification and relapse prevention strategies that may be either psychosocial or psychosocially assisted antagonist treatment, as well as psychosocially assisted opioid substitution treatment, offering a choice of full agonist and partial agonist substitute opioid. Treatment planning should include matching each patient to the most optimal treatment choice for that individual.

The Prevention of and Treatment for Substance Abuse Act, Act 70 of 2008, allows for involuntary treatment of patients with substance use disorders if they are a danger to themselves, their immediate environment, if they pose a major public health risk, cause harm to their welfare or the welfare of their families or others or use crime as a way to sustain their drug habit. Committal through this Act is a time consuming process that starts with a sworn statement to the public prosecutor at the Magistrates court. Outcomes have not been studied in South Africa.

Treatment options:

Relevant pharmacology:

Brief revision of terms:

- Affinity: how tightly a drug binds to a particular target receptor
- Intrinsic activity: the relative ability of a drug-receptor complex to produce a functional response
- Agonist: a drug or neurotransmitter with high intrinsic activity
- Partial agonist: a drug with some, but reduced intrinsic activity, i.e. similar but weaker effect than full agonist
- Antagonist: binds tightly to the receptor and blocks the effect of anything in the agonist spectrum, no intrinsic activity of their own in the absence of an agonist

Full agonist: Methadone:

Methadone is a full mu opioid agonist and NMDA antagonist. It is currently available in two formulations in RSA, namely 5mg/2ml alcohol and sugar containing cough syrup, called Physeptone®, that is not registered or suitable for opioid use disorder treatment and Equity methadone®, a 2mg/ml sugar- and alcohol-free elixir, registered for the treatment of opioid use disorder. Methadone generally has good oral bioavailability and its long half-life (24-36 hours) allows for daily oral dosing, but also leads to accumulation with repeated dosing. Peak plasma levels are reached after about 2-4 hours.

Methadone's full agonist properties lead to concerns about toxicity, which include reduced motor function and respiratory depression. Safety can be improved by cautious initiation with low doses and supervising ingestion of these doses, along with extreme caution with take-home doses, including the use of childproof containers, ensuring lock-up facilities at home and reserving take-home doses for very stable patients. Further safety concerns with methadone include cardiac effects (QTc prolongation with a risk for Torsades du Pointes), especially if high doses are used.²⁴ It is recommended that arrhythmia risk is disclosed to patients and that all patients be screened for structural heart disease, arrhythmia risk and episodes of syncope, before treatment with methadone is commenced. Furthermore, a pre-treatment ECG, a 30-day ECG and the annual ECG testing is recommended, as well as ECG monitoring with doses in excess of 100mg and with unexplained faints or seizures. Clinicians should also be aware of drug interactions that may contribute to QTc prolongation.²⁵

Methadone is metabolised predominantly by CYP 2B6 and 3A4 P₄₅₀ enzymes and caution must be taken with inhibitors of these enzymes, like ketoconazole, fluconazole, ciprofloxacin, erythromycin, certain SSRI's like fluoxetine, paroxetine, sertraline, fluvoxamine and HIV protease inhibitors, as they could result in unexpected toxicity. Enzyme inducers, like rifampicin, St John's Wort, spironolactone, fucidic acid, nevirapine, efavirenz, amprenavir, nelfinavir, ritanavir and certain anticonvulsants decrease methadone levels and may cause unexpected withdrawal or relapse. A reduction in trough methadone levels can also occur in late pregnancy. Synergistic effects, not solely accounted for by metabolic effects, also occur and it is recommended that methadone not be used with benzodiazepines, alcohol or other suppressing drugs.

Because of methadone's full agonist action, it is liable to black-market diversion. Many countries have dealt with this by enforcing strict regulations with regards to methadone substitution treatment (also known as methadone maintenance), which include rigorous

control measures, like special licensing and daily onsite monitoring, and supervised consumption in registered “methadone clinics”. It is thus often used by specialised opioid treatment experts, rather than by general practitioners. Where general practitioners use it, it is recommended that they receive additional training to ensure safe prescription.

Partial agonist: Buprenorphine:

Buprenorphine (Subutex ®) is a partial opioid agonist and kappa antagonist. It has reduced intrinsic activity, compared with a full agonist, and high receptor affinity.²⁶ It is available as a sublingual 2mg or 8mg tablet and its long half-life allows for once daily or even alternate day supervised consumption. Peak plasma levels are achieved after approximately 90 minutes. Individuals report a 'clearer head' with buprenorphine, in contrast to the mental 'clouding' sometimes experienced with methadone.

One of the biggest concerns with black-market diversion of substitution opioids is the risk of serious toxicity, especially if ingested by non-tolerant individuals like children. The maximum effect that buprenorphine can produce is lower than that of a full agonist and this ceiling effect results in significantly reduced risk for toxicity, even for non-tolerant individuals, thus reducing overdose risk and making it more useful for office-based practice. Although Buprenorphine can cause slight respiratory depression, there is a limit to this, so that the maximum depressant effect does not pose a risk when used alone under therapeutic conditions. It binds tightly to receptors and is difficult to displace, further improving its safety profile if a full agonist, like heroin, is used “on top”. There have, however, been rare reports of deaths from overdose, usually when oral formulations are used intravenously and with other depressant substances, like benzodiazepines due to a synergistic effect with these substances.²⁷

Buprenorphine can precipitate withdrawal in an individual dependent on a full mu agonist because of its lower intrinsic activity and high receptor affinity. The likelihood of this happening depends on the level of tolerance (i.e. the amount of drug used), time since last administration and half-life of the drug and dose of buprenorphine used. It is thus recommended that the prescriber allow for sufficient time after the last dose of the drug (e.g. until clear objective evidence of early withdrawal) and makes use of a slow and gradual buprenorphine dose induction.

Buprenorphine, similarly to methadone, is metabolised by CYP 3A4 P₄₅₀ enzymes and monitoring and dose adjustments may be required if used with inducers or inhibitors of these drugs. These interactions are less often clinically relevant, compared to methadone.

Careful titration of dose is required in cases with liver impairment. Cases of liver abnormalities have been noted, especially with intravenous use of buprenorphine and in patients with underlying liver problems. Periodic monitoring of liver functions are thus indicated, especially in patients with underlying viral hepatitis or other liver problems.

Partial agonist that includes deterrent to intravenous abuse: Buprenorphine-Naloxone combination:

Initial reports suggested that buprenorphine would have low abuse potential.²⁸ However, parenteral abuse and black-market diversion have been reported worldwide.²⁹ Tablets are crushed and diluted and then administered intravenously. This practice places the user at risk for various health problems, including transmission of blood borne viruses. Therefore, the

buprenorphine-naloxone combination tablet was developed as a strategy to prevent injecting use of buprenorphine.

Naloxone has low sublingual absorption, whereas buprenorphine has reasonably good absorption sublingually. If naloxone is administered parentally to a tolerant opiate dependent individual, rapid and unpleasant withdrawal symptoms ensue in most patients. The combination tablet is therefore an effective deterrent to injecting use in many patients. Studies have shown that a 4:1 ratio of buprenorphine-naloxone, is able to precipitate a highly unpleasant, but relatively safe withdrawal if given intravenously in most individuals, but is as effective in preventing withdrawal as sublingual buprenorphine alone.³⁰ This combination is available in South Africa as Suboxone®. Although not everyone has this deterrent effect when injecting the prescribed medication, the combination tablet is more effective than buprenorphine alone in preventing injecting use and significantly reduces its diversion potential.

Antagonist (short-acting): Naloxone (Narcan®):

Naloxone is a non-selective, short acting opioid antagonist. It has very high affinity for the mu opioid receptor and is frequently used in the treatment of overdoses. It is usually administered via a parenteral route (intravenous/intramuscular), but can also be administered intranasally.

Antagonist (long-acting): Naltrexone:

Naltrexone (Naltima®) is a specific, orally active, long-acting opioid antagonist. It has a high affinity for the mu opioid receptor, without any intrinsic activity and thereby effectively blocks the effects of any abused opioid. Plasma concentrations peak one hour after oral administration and its half-life varies between 2 and 6 hours. Its active metabolite has a longer half-life and also has antagonist effects.

Extended release Naltrexone formulations are also available abroad, including injectable (Vivitol®) or implantable slow release formulations. These sustained release formulations are not registered in South Africa, although some individuals import the implants. Currently, the importation of extended release Naltrexone preparations into South Africa requires prior MCC approval for each individual patient.

Treatment of withdrawal:

Opioid withdrawal is rarely dangerous, unless the patient is pregnant (risk of spontaneous abortion or preterm delivery) or physically compromised. It is however a highly unpleasant syndrome and it would not be ethical to force patients to go through withdrawal without the option of medical detoxification to alleviate this. Opioid detoxification is a medical process that involves a graded and controlled reduction in tolerance to opioids, thereby minimising unpleasant withdrawal symptoms. It is the first step of treatment where the aim is an opioid free approach. It is not a stand-alone treatment since most patients relapse rapidly back to opioid use, when medication is stopped¹⁵; it is rather an initial intervention that allows the addict to engage in the most important step of treatment, namely relapse prevention. Relapse prevention includes psychosocial treatment and may also include the use of an opioid antagonist, like Naltrexone.

Prior to detoxification, patients should be well prepared and motivated and a treatment plan should be put in place. During detoxification, total abstinence is achieved, usually over 7-21

days. Patients should be warned to expect a degree of discomfort, but should not be allowed to suffer unnecessarily. The clinical picture, rather than the history should determine treatment during detoxification.

In- or outpatient?

Detoxification can be done on an in- or outpatient basis. Outpatient detoxification is usually used for patients with low levels of tolerance or for detoxification from low potency opioids or with slow and gradual tapering often following a period of substitution treatment. Detoxification over a short period of time (about 7-10 days) may be attempted on an outpatient basis in a highly motivated patient, with a good support structure, using a partial agonist; however, short-term success is often better with inpatient detoxification. Comorbid medical or psychiatric problems or concurrent withdrawal from alcohol or benzodiazepines, are also indications for inpatient detoxification. Inpatient detoxification does increase treatment cost and although short-term outcomes seem better, evidence for long-term advantages, like improved long-term abstinence or treatment retention is lacking.¹⁵

Pharmacological options:

With mild withdrawal, i.e. withdrawal in cases of low tolerance, e.g. less frequent use of smaller amounts of opioids or low potency opioids, or if the patient chooses an opioid free detoxification, medications that provide symptomatic relief are usually used. The alpha-2 agonist, e.g. clonidine,³¹ is used, along with a number of other symptomatic treatments (e.g. analgesics, anti-emetics, anti-diarrhoeal drugs, anxiolytics, hypnotics etc.).

Moderate to severe withdrawal usually requires the use of an opioid substitute. This may be either a full agonist (e.g. methadone) or a partial agonist (e.g. buprenorphine), which is prescribed at a dose that alleviates withdrawal symptoms without causing intoxication (the 'baseline dose'). With a long-acting full agonist, like methadone³², where the risk of early toxicity is significant, the baseline dose is carefully established in the 1st 2 to 3 days and is then gradually reduced usually over a period of 1-3 weeks, allowing the level of tolerance to normalise in a manner that is tolerable for the addict. Patients often continue to experience a degree of discomfort for a further 7 to 14 days. This is the main limitation of using Methadone for detoxification over a short timespan (e.g. during inpatient detoxification). With a partial agonist like buprenorphine³³ or buprenorphine/naloxone³⁴, where risk of toxicity is low, but there is a risk of precipitated withdrawal or early treatment drop-out, induction is done using low doses initially, but rapidly increasing to the baseline dose.

When comparing methadone and buprenorphine for detoxification, it seems that patients experience more severe withdrawal early in withdrawal on buprenorphine compared to methadone, but that significantly less at completion of dosing regimens. Methadone seems to be associated with higher peak and more prolonged rebound withdrawal than buprenorphine, when comparing short dosing regimens. Completion rates appear to be similar.³⁵ Some patients may choose to transfer to substitution treatment after starting a detoxification program, and if this option is available to them, it should always be considered.

Accelerated, rapid, or ultra-rapid withdrawal refers to the use of an opioid antagonist to induce withdrawal in order to shorten the duration of withdrawal. This is usually done while the patient is given heavy sedation or anaesthesia. These techniques are not associated with better long-term outcomes and have been associated with adverse effects and are thus not recommended.^{17, 36}

Overdose risk is greatest after periods of abstinence where the individual has lost tolerance, like relapse after an opioid free treatment episode, incarceration or hospitalisation. Patients should be warned about this risk following detoxification.

Withdrawal may be complicated in patients who also have tolerance for other substances, especially GABA agonists, like benzodiazepines or alcohol. These patients may be mistaken for being in opioid withdrawal, when in fact they may be withdrawing from these other concomitant substances. This requires a detailed assessment, and carefully integrated management.

See appendix B for suggested guidelines for detoxification

Relapse prevention:

Psychosocial interventions:

Psychosocial interventions refer to a broad range of ancillary interventions, including social support (which includes addressing basic needs) as well as a wide range of psychological interventions (including unstructured supportive therapy, motivational interviewing, as well as structured interventions, like contingency management or cognitive behavioural therapy.) Whether a patient and doctor/treatment team decide on detoxification and psychosocial treatment alone, or decide to use a pharmacological relapse prevention strategy, ancillary psychosocial support for all patients is indicated and strongly advised. Increased social support is associated with better outcomes.³⁷

Various psychosocial interventions are used to provide individuals in recovery with motivation and skills to maintain sobriety and there is evidence to support the use of cognitive behavioural therapies, behavioural interventions like contingency management or community reinforcement approach and motivational enhancement therapy. Less well studied, but with empirical evidence for support, is the spiritual 12-step programs and therapeutic communities. Other helpful interventions include vocational training, housing, self-help groups, family therapy, etc.

Several studies have shown that longer duration in drug treatment is associated with better outcomes than shorter treatment episodes and efforts to improve treatment retention are thus important.³⁸ The ATOS study also showed that the first three months (initiation into treatment) were especially very important. Furthermore, although treatment dose (i.e. total days in treatment) was important; successful completion of treatment was predictive of better outcomes; independent of total days spent in treatment and retention in treatment is therefore critical. ATOS also confirmed the need for long-term programs.³⁹

Opioid use disorder is a chronic, relapsing disorder and relapse is common and not unexpected. Relapse can be viewed as a learning and growth opportunity. Many clients find that engaging in an aftercare program (for example self-help support groups like Narcotics Anonymous), provide them with a useful support structure and may reduce relapse.

Psychosocially assisted pharmacotherapy:

Opioid substitution treatment (OST)

Given the chronic, relapsing nature of opioid use disorders and the frequently poor results of detoxification, followed by only psychosocial treatment, a useful strategy is to allow patients to stabilize their lives by using a substitute opioid. This approach had been widely used ever since the first landmark study by Dole and Nyswander was published in 1965.⁴⁰ Although this strategy is not widely used and accepted in South Africa, substitution prescription of opioids is a well-established treatment option internationally. A large body of research literature and clinical practice supports this intervention.^{41,42} Cochrane reviews confirm that maintenance treatment with methadone⁴³ and buprenorphine^{44,45} have proven effectiveness, provided that adequate dosages are prescribed and appropriate supervision is given. In practice, most patients on OST will stop heroin use or only use infrequently. Only about 20-30% practice ongoing regular heroin use.⁴⁶ It has been shown to decrease illicit opiate use and to reduce the incidence of high-risk and unlawful behaviours associated with opioid use disorder.^{47,48,49} These include reduced morbidity⁵⁰ (including HIV risk,⁵¹ incarceration⁵², and other substance use⁵³), mortality⁵⁴ associated with heroin use disorder and improved treatment retention. Compared to detoxification and psychosocial interventions, OST has been shown to produce better outcomes.⁵⁵ Furthermore, OST increases legitimate earnings, employment and other indicators of improved social functioning. It is thus not surprising that both methadone and buprenorphine are on the WHO's essential drug list.⁵⁶

OST is not only effective, but it is also less expensive than alternatives such as not treating or incarceration.⁵⁷ It has been estimated that for every dollar invested in opioid treatment, between \$4 and \$7 is saved in reducing crime, criminal justice costs and theft. When healthcare savings are included, this is increased to 12:1.⁵⁶

Substitution treatment is suitable for addicts who are willing to give up the “high” and want to stop illicit opioid use, but who are unable to achieve abstinence from all opioids at the current time. They receive an individualised prescribed dose of methadone or buprenorphine at a suitable dose to suppress withdrawal and craving and to prevent the ‘high’ if illicit opioids are used on top. With buprenorphine, this is achieved when the dose is high enough to ensure high receptor occupation and thus blocking of extra abused opioids. In the case of methadone, if it is given at a high enough dose, cross-tolerance develops, thereby blocking the euphoric effects of any abused opioids.

OST has many advantages for the patient; they change identity from addict to patient, visit a doctor and pharmacy rather than an illicit drug dealer, move away from black market opioids, which has potential contaminants, variable purity, is of an uncertain supply and is illegal with the risk of arrest and is expensive to acquire. Furthermore, the abused opioid usually has a short half-life and the user fluctuates rapidly between intoxication and withdrawal, often several times a day as the central nervous system concentrations rapidly rise and fall. With OST, the medication is slowly absorbed and has a long half-life, thus reducing these fluctuations between peak and trough, with a resultant effect where the individual feels “normal” rather than intoxicated and in withdrawal and this allows them to improve their functioning and wellbeing. It provides the person the opportunity to stabilise their lifestyle, develop insight and reduce harm from illicit drug use. This stable opioid effect is also associated with improved neonatal care in pregnant mothers.

There is evidence to recommend that higher doses of substitute opioid be used as they fare better than lower doses in retaining patients in treatment and in preventing illicit heroin use. With methadone, doses above 60mg have better outcomes than lower doses and treatment doses and a dose of 60-120mg is recommended.⁵⁷ When Buprenorphine is used, it is suggested that doses of 8-16mg have better outcomes than doses below 8g, with 16mg having better outcomes than 8mg.⁵⁷ The optimum recommended dose is 12-24mg.⁵⁸ Within the South African context; many patients are under-medicated because they are unable to afford optimum dosing.

When Buprenorphine is used, it is important for patients to wait until they experience objective evidence of mild to moderate withdrawal symptoms, and to start with a low dose, in order to avoid precipitated withdrawal, but then to rapidly increase the dose, in order to retain the patient in treatment. In contrast, methadone's long half-life is associated with accumulation and the risk for toxicity that is highest in the first 2 weeks and when using methadone, it is important to start low and increase very cautiously and slowly. With both methadone and buprenorphine, it is important to continue to gradually increase the dose until opioid craving, illicit opioid use, and withdrawal symptoms have abated or excessive side-effects (like sedation, constipation etc.) are experienced.

Buprenorphine-naloxone allows for less tight supervision of consumption and earlier take-home medication. If a patient begins to test positive for illicit opioids after a prolonged period of stability on a substitution drug, it requires careful evaluation. There may be several reasons for this, e.g. there may be a new prescription e.g. a CYP3A4 inducer, which is causing insufficient opioid blockade and the need for top-up doses with illicit opioids. The possibility that the patient has relapsed and that prescribed medication is diverted, however, also needs to be considered.

Diversion risk and supervised consumption:

Diversion of substitution opioids is an ongoing risk and in order to minimise this, tight supervision and on-going supervised consumption is required with methadone and buprenorphine alone. Within the South African context, where there are no state run specialised clinics where patients can receive substitution medication under daily supervision, the safe option is to make use of a pharmacy that is willing to supervise the taking of medication on a daily basis. Pharmacies need clear instructions of what is expected of them and who to contact in case of any concerns. There are inherent concerns when family members or friends are used to supervise medication: drug addicts are skilled in convincing loved ones to do things they don't wish to do; furthermore medication dosing may be used as leverage for the supervisor's own agenda. An impartial trained professional, like a pharmacist or practice nurse is thus the preferred supervisor.

Gradual initiation of take-home doses can be used as reward incentive for sustained clean urines and evidence of a stable life-style. Patients who receive Buprenorphine-Naloxone also need close supervision, especially initially, but in most cases do not require supervised consumption. It is safer and seems to have less diversion potential and this less tight supervision of consumption translates to significantly cheaper treatment.⁵⁹ Extended release buprenorphine formulations and non-removable film formulations to improve compliance of buprenorphine are not yet available in South Africa.

Despite the reduced risk of misuse and diversion, cases of buprenorphine-naloxone diversion have been reported and on-going monitoring in this regard is required. The main cause for this is suboptimal dosing. As with other substitution opioids, high enough doses should be used to suppress withdrawal and cravings.

Choice of substitution opioid:

Buprenorphine has an advanced safety profile over methadone; evidence for this comes from France, where buprenorphine was rolled out without restrictions in 1996 and methadone was approved at approximately about the same time. Methadone use was however restricted to highly regulated clinics. A review of buprenorphine- vs. methadone-related deaths in this country found that the number of buprenorphine prescriptions exceeded methadone 10 times, but in contrast, the death rate associated with buprenorphine was only 1,4 times that for methadone for the same period. Deaths on buprenorphine were associated with intravenous misuse of the sublingual formulation, in conjunction with other CNS depressants. Fatal overdoses with methadone alone occurred and the co-administration of other CNS depressants magnified the risk. Furthermore, since the wide and unrestricted rollout of buprenorphine in France, their opiate-related death rate has decreased.^{60, 61}

Various head-to-head studies have compared methadone and buprenorphine and while some have hinted at superiority for methadone at retaining patient in treatment, others have shown equivalence in preventing non-prescribed opioid use. Adequate dosing and flexibility in regimes have limited comparability in treatment regimes.¹⁵ The choice of substitute opioid is a clinical decision that takes into consideration among other things prior response, medical or mental health comorbidity, possible drug interactions, side-effect profile, cost/accessibility, use of other drugs, patient choice, etc. and is made in conjunction with the patient. Some patients prefer the “dulling” effect of methadone, while others find the daily supervised dosing, too tedious and interfering with their day-to-day functioning.

In view of the added safety benefit, the buprenorphine-naloxone combination is a useful and safe first-line option for opioid substitution treatment. Buprenorphine is useful in cases where the added naloxone is contra-indicated (e.g. pregnancy) or not tolerated. It might be more difficult to begin treatment with buprenorphine or buprenorphine-naloxone in highly dependent patients and methadone may be more useful in this patient group. Some patients may benefit from the structure of daily-supervised consumption, while for others this is a deterrent to treatment or interferes with employment. Furthermore, treatment failure or contra-indications to buprenorphine-naloxone or buprenorphine are indications for choosing methadone. Indications for changing from methadone to buprenorphine or buprenorphine-naloxone include intolerable side-effects on methadone, patients who have done poorly on methadone, if patients wish to change or if clinician feels that a change is indicated, e.g. injecting use of prescribed medication, ECG changes, wish to consume medication without supervision, improved safety profile, concerns about drug-interactions, etc. Similarly, indications for a change to methadone include poor response, side effects or diversion of medication with need for increased supervision, etc.

Co-prescribing of benzodiazepines:

Although co-prescribing of benzodiazepines with OST is frowned upon, it is not uncommon. Some prescribers use benzodiazepines to reduce treatment costs, by using it to reduce substitute opioid dose. Others prescribe at the insistence of patients, to aid with insomnia, to cope with day-to-day stress or to medicate an underlying anxiety disorder. Prescribers are

advised that this is *not good practice* and it should be avoided where possible. Not only are the benzodiazepines associated with unwanted side-effects, like impaired judgement, memory, cognition and sleep architecture, but it also increases the risk of overdose and the risk from complications from injecting use of the benzodiazepines. Furthermore, benzodiazepines are addictive drugs; they are associated with tolerance, withdrawal and dependence and often lead to cross- addiction or co-addiction.

Regulation of opioid substitution treatment:

Important elements of substitution prescribing include regular monitoring of patients, random drug screening to pick up relapse to illicit opioids and use of other addictive substances, and ongoing psychosocial interventions.⁶²

Substitution prescription does pose the risk of multiple problems if unregulated, and these include the potential for unsafe or unethical practices by medical professionals that may lead to diversion of prescribed medication or even unnecessary fatalities. It is thus strongly advised that any doctor who chooses to do substitution prescribing, attend an accredited training course. There is currently no legislation in this regard, and self-regulation is thus essential. It is recommended that training courses with an evaluation component are used for accreditation of treatment providers and that only accredited prescribers be funded for the provision of substitution treatment.

Opioid substitution treatment is an effective and cost-effective treatment for opioid use disorders.⁵³ As such it recommended that healthcare funders include it in their package of benefits. A remuneration package should be agreed upon for substitution prescribing that includes drug testing, counselling and other ancillary support. Although over-servicing of patients should be avoided, flexibility is important. Some clients (especially those with co-morbid medical or mental health problems) may require more support, drug testing and supervision and the average number of doctor's visits is likely to be higher in cases where no practice nurse or counsellors are available.

Diversion of medication to the black-market with the risk of unnecessary death remains a valid concern and adequate supervision of patients with regard to opioid dispensing and consumption, especially with methadone and buprenorphine, is essential.

Another concern is that patients may see more than one doctor in order to divert the extra medication. A patient register would help to prevent this "doctor shopping" and "pharmacy hopping". Until such a register is available, prescribers should be aware of this risk and any suspicion of diversion should be thoroughly investigated and dealt with.

How long to continue?

The ultimate aim of opioid substitution treatment is eventual dose reduction and abstinence when the individual is ready. Treatment goals should be reviewed every 6-12 months. There are no studies that have looked at the optimal duration of OST. Longer treatment is associated with better outcomes (lower rates of relapse to illicit opioid use, increased survival rates) and treatment should be viewed as open-ended and continued as long as clinically indicated. Ideally, discontinuation should not be considered before the patients have achieved significant personal changes that may include employment, meaningful alternative activities and regular social contact and support from non-users. Most patients need a minimum 1-year of treatment, many need longer treatment and some patients require life-long substitution therapy.

(See appendix B for suggested guidelines for buprenorphine / buprenorphine-naloxone and methadone substitution prescribing)

Opioid free pharmacotherapy: Antagonist treatment:

There are limited opioid-free pharmacological interventions available. Naltrexone is an opioid antagonist that blocks opioid receptors without producing an effect. This makes it difficult to get high from an abused opioid, thereby allowing the patient to stabilise their lifestyle. An oral dose of 50mg effectively blocks the opioid receptor for about 24 hours.

The greatest problem with oral Naltrexone is compliance and treatment retention. Compliance problems with oral Naltrexone can be overcome by supervising consumption or by using the injectable or implant slow release formulations.⁶³

There have been reported concerns about increased rates of overdose in the period following cessation from Naltrexone use and patients who use this medication, should be educated around the loss of tolerance. Analgesia that requires opioid treatment (e.g. following surgery or severe trauma) may also be problematic to manage in patients on Naltrexone. Prescribers should be conscious about the risk that patients may be coerced into treatment with Naltrexone. It has been suggested that earlier stages of opioid use disorder respond better to Naltrexone than late stages. This treatment option should also be considered in patients who are more likely to be successful with sobriety, like employed patients, those under threat of legal sanction and those with less severe addiction and shorter addiction histories, including younger patients.¹⁵ There is also preliminary evidence that Naltrexone may also add benefit in reducing the use of other drugs and in patients with poly-drug use.⁶⁴

(See appendix B for suggested guidelines on Naltrexone use)

Treatment of overdose:

Overdose is a common cause of death in heroin addiction. Patients at particular risk of overdose include youth, those relapsing after abstinence-oriented treatment and those recently released from prison.^{65,66} Patients with opioid overdose present clinically with myosis, respiratory depression and coma. The short acting opioid antagonist, Naloxone, is first line treatment for opioid overdoses. It is only pharmacologically active following parenteral injection. Multiple dosing may be needed if the illicit opioid has a longer duration of action than Naloxone. Since most overdoses take place in the presence of others, some studies have found that education about overdose risk and take-home Naloxone can prevent overdose.

Special populations:

The treatment of opioid use disorders is more complex in a number of special populations, including children and adolescents, women, especially during pregnancy and breast feeding or mothers with small children, patients with medical comorbidity especially hepatic impairment, HIV or tuberculosis and patients with complex psychiatric comorbidity or in patients with chronic pain, that are dependent on prescription opioids. Management of these patients often requires the expertise of a specialist in the treatment of opioid use disorders.

Conclusion:

Opioid use disorders in South Africa is growing. It is important that clinicians become knowledgeable about the role that responsible use of pharmacotherapy can play in aiding

patients to achieve and maintain sobriety. It is emphasised that these are not stand-alone treatments. The treatment of opioid use disorders requires an evidenced based multidisciplinary approach that may include psychotherapeutic and social interventions.

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Appendix A:

1. Signs and symptoms of opioid intoxication
2. Signs and symptoms of opioid withdrawal
3. Assessment of the opioid addict

1. Signs and symptoms of opioid intoxication

- Euphoria, profound relief from anxiety and tension, followed by apathy
- Initial mild brief increased energy, followed by psychomotor retardation
- “Nodding”- state between arousal and sleep, where individual is rousable
- Pupillary constriction
- Hypoactive bowels, constipation
- Slow regular respiration, ↓ coughing, risk of respiratory depression
- Slurred speech
- Impaired judgement, concentration, memory
- Dulling of pain
- Difficulty with passing urine
- Nausea and vomiting
- Sweating, warm flushing of the skin, itching
- Dry mouth
- Rarely convulsions
- Large doses of heroin may result in a potentially lethal overdose

Various rating scales are available to estimate the severity of withdrawal. They are useful to ensure that the individual is in withdrawal prior to prescribing substitution opioid medication for detoxification, and to monitor progress. (*See rating scales below, Appendix D*)

2. Signs and symptoms of opioid withdrawal:

<u>SYMPTOMS</u>	<u>SIGNS</u>
Looks like a ‘flu-like’ illness	
Abdominal cramps	Diarrhoea
Anxiety	Increased blood pressure
Craving	Increased pulse
Irritability, dysphoria	Lacrimation
Fatigue	Muscle spasms
Hot and cold flushes	dilated pupils
Muscle aches	Pilo-erection
Nausea, sweating	Rhinorrhoea
Restlessness	Vomiting

The onset and duration of withdrawal depends on the half-life of the abused opioid.

Rough estimates of first appearance of withdrawal, peak and duration of withdrawal:

<u>Drug</u>	<u>Time to withdrawal</u>	<u>Peak</u>	<u>Duration</u>
Pethidine	4 – 6 hours	8 – 12 hours	
Heroin	6 – 12 hours	36 – 72 hours	5-10 days
Morphine	8 – 20 hours		
Codeine	24 hours		
Methadone	36 – 72 hours	72 – 96 hours	up to 3 weeks

Methadone abstinence syndrome develops more slowly and is more prolonged but usually less intense than other opiate abstinence syndromes. These are average times only. In practice, it may take longer or shorter for withdrawal to start, peak or subside. Treat the withdrawal symptoms rather than the drug history.

3. Assessment of the opioid addict:

- Every patient who requires an intervention for opioid dependence needs to have a detailed assessment, to identify complications and formulate treatment goals.
- The assessment should include building a trusting therapeutic relationship.
- Enquire about what precipitated the consultation and the person's expectations, including short, medium and long-term goals
- Assessment should include determining medical, psychological and social needs of the patient.
- Take a history to determine:
 - Opioids used: type (including prescription opioids and substitution opioids), quantity, frequency, route, duration of current episode (corroborate if possible)
 - Does the patient have a Naltrexone implant or use Naltrexone tablets
 - The other substances used, including route, dosage, duration of use
 - Degree of dependence, distinguish from non-dependent abuse/use
 - Medical history, including history of accidental overdose, diseases from drug use (like abscesses, endocarditis, deep vein thrombosis), other conditions, current medications (consider drug-interactions with medications for opioid use)
 - Psychiatric history
 - Risk behaviour, including sharing of equipment and high risk sexual behaviour; Hepatitis A, B or C, and HIV status - if known
 - Forensic history, legal status
 - Social history – including employment, housing, financial, family
 - Previous treatment episodes/ rehabilitation centres attended, periods of abstinence
 - What precipitated the relapse (if relapsed)
 - Trigger for treatment, motivation to stop or change pattern of use
- Examine for:
 - Evidence of drug use (e.g. needle tracks, signs of drug intoxication or withdrawal)
 - The presence of complications (e.g. poor nutrition, anaemia, skin abscess, thrombophlebitis, liver disease, HIV, chest infection, tuberculosis etc.)
- Assess mental health and refer to a Psychiatrist if indicated

- Discuss harm reduction:
 - Discuss safer sex
 - Risk of accidental overdose
 - Risk of blood-borne infections
 - Offer testing for infections i.e. hepatitis A, B, C and HIV (informed consent)
 - Offer hepatitis B vaccine
- Do urine or saliva drug test -results should be interpreted in the light of clinical findings, as false negatives and false positives can occur.
 - False positives can be caused by the use of loperamide, quinolones and over-the-counter medicines that contain codeine.
 - Negative results occur in people on synthetic opioids or may occur during pregnancy.
 - A negative result brings current dependence into doubt.
 - Repeat the urine test, as false negatives do occur.
 - On-site urine-testing strips provide a basic non-quantitative guide to the class of drugs currently used. If the test is positive and the person has obvious signs of opioid use (e.g. track marks, signs of withdrawal), it may be used as a confirmatory test for opioid use.
 - Mouth swab tests: Mouth swab tests (oral mucosal transudate) provide information about recent drug use, but there is a shorter detection window (when heroin has been taken, it can be detected up to 4 days later with urine tests but only up to 24-48 hours later with mouth swabs).
 - Urinalysis carried out in a laboratory is the most reliable confirmatory test and if there is any doubt about a result, it should be used. It is usually done by gas chromatography and although accurate, has the disadvantages of being more costly and takes longer before receiving a result.
- Consider investigations to exclude complications. Choice of investigations is guided by clinical judgement, and may include:
 - Full blood count (to exclude anaemia, signs of infection)
 - Liver function tests (hepatitis or high intake of alcohol may cause abnormalities, before starting buprenorphine substitution)
 - Electrolytes (to assess renal function)
 - Tests for hepatitis A, B, or C and HIV (pre-test and post test counselling required)
- Is there convincing evidence of dependence? (Is the person taking drugs regularly? - daily use is an indicator of dependence) Is there evidence of neuro-adaptation, i.e. tolerance and withdrawal?
- Discuss the treatment options and agree on treatment goals and a management/treatment plan/programme
 - Detoxification and relapse prevention
 - Substitution therapy if appropriate
 - Harm reduction options if available

Appendix B:

1. Guidelines for short detoxification from all opioids
 - (i) Using methadone (inpatient treatment recommended)
 - (ii) Using buprenorphine or buprenorphine-naloxone combination
 - Inpatient detoxification
 - Outpatient detoxification
 - (iii) Using clonidine
 - (iv) Using symptomatic treatment
2. Guidelines for the use of naltrexone
3. Guidelines for substitution prescribing
 - (i) Using buprenorphine
 - (ii) Using methadone
4. Guidelines for transferring a patient from methadone to buprenorphine or buprenorphine-naloxone combination
5. Guidelines for transferring a patient from buprenorphine to buprenorphine-naloxone
6. Guidelines for transferring the patient from buprenorphine/ buprenorphine-naloxone to methadone

1. Suggested guidelines for short detoxification, with rapid total abstinence from all opioids:

- Complete detailed assessment (see appendix A)
- Outpatient detoxification should only be considered in selected cases where it is considered safe to do so (considering the risk of relapse back to abused opioid as well as risk of diversion, overdose and death). Other factors to consider include transport, level of motivation, comorbidity and social support. An infrastructure for daily-supervised consumption of methadone or buprenorphine and regular follow-up and monitoring and random drug testing is required for outpatient detoxification. High levels of opioid tolerance, poly-drug use, and other co-morbidities indicate a need for inpatient detoxification.
- Inpatient detoxification is particularly appropriate during pregnancy and it should ideally be timed for the mid-trimester. Long-term supervised care is important during pregnancy and most experts recommend substitute prescribing. There is no clinical data on the use of the combination tablet Buprenorphine-Naloxone in pregnancy and this should be avoided.
- Negotiate a treatment contract with the patient.
- Patients should be educated that their level of tolerance is reduced during detoxification. The dose of illicit opioid that was used prior to detoxification may subsequently cause overdose.

1(i): Methadone:

- Patients should present in early withdrawal – i.e. roughly 8-12 hours after last use, use of a rating scale is recommended
- The baseline dose of methadone is determined by giving the patient small incremental doses of methadone until a dose is determined that alleviates signs of withdrawal without causing signs of intoxication. Once stabilised on this dose, it can then be gradually reduced.

Outpatient regime:

Outpatient methadone detoxification involves a risk of accidental overdose and thus requires skill and expertise. It is recommended that outpatient methadone detoxification is only used by doctors who have received appropriate training to ensure it is done safely. Buprenorphine preparations may be a safer choice.

Inpatient regime:

Day 1:

- **VERY IMPORTANT:** Ensure the patient is in withdrawal because of risk of overdose (use of a rating scale recommended)
- Give Methadone 5-10 mg orally (supervise consumption) and watch for signs of intoxication (especially pinpoint pupils or drowsiness)
- If after 2 hours objective withdrawal symptoms are still present, give another 5-10 mg orally
- Wait another 2 hours, if still objectively symptomatic, repeat 5-10 mg for the last time
- Initial dose to suppress withdrawal symptoms can be repeated after 12 hours if symptoms re-emerge
- Total dose in first 24 hours should not exceed 30mg, unless at the recommendation of an expert in the treatment of opioid use disorders

Day 2 onwards until baseline dose is determined:

- Repeat total dose of day 1 as a single or divided doses (usually a twice daily dose)
- Watch for objective signs for withdrawal. If present, the daily dose may be increased by 5-10 mg. Watch for signs of intoxication
- This can be repeated daily (2-3 days) until the dose that prevents objective opioid withdrawal symptoms is determined
- The dose prescribed the previous day is then the baseline dose

From baseline dose onwards:

- Decrease by 10-20% of baseline dose daily or alternate days
- If patient's withdrawal symptoms allow it, the withdrawal regime may be shortened
- Use non-substitute medication (see below) for any additional symptoms.

1(ii): Buprenorphine or Buprenorphine- Naloxone combination

- Buprenorphine is a partial opioid receptor agonist and is a safer alternative than methadone for opioid withdrawal. It has a ceiling effect, after which it acts as an antagonist, blocking the effects of further doses or other opioid agonists (like heroin)
- It is important that buprenorphine be prescribed correctly, as it has the ability to precipitate opioid withdrawal in certain circumstances. In intoxicated patients and those who still have enough abused opioid in their system to prevent withdrawal, buprenorphine will have a higher affinity for opioid receptors than the full opioid agonist, (e.g. heroin or methadone) and may displace them. It has lower intrinsic activity than these agonists do, and because of this, it will act like an opioid antagonist and precipitate withdrawal.
- Buprenorphine dissociates slowly from the μ - opioid receptors giving it a long period of action. This helps to reduce withdrawal symptoms during dose reduction and blocks the effects of other opioids.

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- Buprenorphine is safer than methadone, but should not be used unsupervised with other sedative drugs, especially benzodiazepines, alcohol and other opioid drugs, as this can result in a potential overdose. Always warn patients about this risk.
- Buprenorphine-naloxone delivers the same performance as an equivalent dose of buprenorphine alone. It has lower abuse potential and is thus the preferred medication for any patient whose intake of medication is not supervised. If buprenorphine-naloxone is used, dose equivalents to buprenorphine alone, can be used. Example: 4mg of Buprenorphine equals 4/1mg of buprenorphine-naloxone; 8mg equals 8/2mg etc.
- It is recommended that consumption be supervised daily, unless the combination tablet is used. All patients however require daily medical review during the first few days of detoxification. (See appendix C)
- Some patients are keen to reduce and stop opioid use as soon as possible, while others struggle with a short detoxification regime (5-7 days) and prefer a slower detoxification period, where the dose is very slowly tapered over a longer period of time (up to 21 days).

Outpatient withdrawal over short period of time:

Australian department of health recommend regime for short outpatient withdrawal

(Patients should be reviewed medically on a daily basis)

	Proposed regime	Recommended lower and upper limits
Day 1	6 mg	4-8 mg
Day 2	8 mg	4-12 mg
Day 3	10 mg	4-16 mg
Day 4	8 mg	2-12 mg
Day 5	4 mg	0-8 mg
Day 6		0-4 mg
Day 7		0-2 mg
Day 8		0-1 mg

Inpatient withdrawal over short period of time:

Australian department of health recommend regime for inpatient withdrawal

	Proposed regime	Total daily dose
Day 1	4 mg at onset of withdrawal and 2-4 mg evening dose PRN.	4-8 mg
Day 2	4 mg mane, 2-4 mg nocte PRN.	4-8 mg
Day 3	4 mg mane, 2 mg nocte PRN	4- 6 mg
Day 4	2 mg mane, 2 mg nocte PRN	2-4 mg
Day 5	2 mg PRN	0-2 mg
Day 6	No dose	
Day 7	No dose	

Both these regimes are only rough guidelines. Some patients may require lower doses of medication. With high levels of tolerance, some patients require higher doses of buprenorphine or Buprenorphine-Naloxone (up to 16 mg or 16/4mg /day).

Please note that a slower detoxification phase, over a longer period of time, is also possible and is often used if patients find above regimes too uncomfortable. This is especially true for outpatients.

Non-substitute medication for detoxification:

- Non-substitute prescribing is indicated in patients who choose a non-opioid withdrawal regime or who only experience mild withdrawal symptoms
- Non-substitute, symptom relieving medications can be used in conjunction with substitution medications in order to reduce the daily opioid requirements

1(iii): Clonidine:

Clonidine (Dixarit®) is a medication marketed for the treatment of hypertension used for many years to treat the sympathetic hyper arousal that occurs in opioid withdrawal. It is most effective when used for detoxification in an inpatient setting because of potential side effects.

Advantages include:

- It is not a scheduled medication
- The use of opioids can be discontinued immediately
- It does not produce opioid euphoria and is not addictive

Although Clonidine alleviates some symptoms of opioid withdrawal, it is not effective for muscle aches, insomnia or drug craving. These symptoms require additional medication (see symptomatic medication below).

- Ensure patient does not have blood pressure or cardiac abnormalities
- Give a test dose of 50 micrograms orally or sublingually (75 micrograms may be used for patients weighing more than 80 kg)

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- Measure the patient's blood pressure after 30 minutes. If diastolic blood pressure is normal and there is orthostatic hypotension (a drop in systolic blood pressure of 10 mmHg upon standing), the patient may continue the regime
- Clonidine 75-150 micrograms orally 6 hourly may be used
- Taper this dose over 4-6 days

1(iv): Other symptomatic treatment:

- Heroin withdrawal is highly uncomfortable, but it is not dangerous (except in physically compromised patients and during pregnancy). It is associated with various physical complaints and these can be treated symptomatically, providing they are not severe. Symptomatic treatment can also be used as an adjunct to substitute prescribing or Clonidine. These drugs are not registered for the treatment of opioid withdrawal and use is therefore off-label for this indication.

Examples include:

- An antispasmodic like hyoscine butyl bromide (Buscopan®) for the abdominal cramps
- Non-steroidal anti-inflammatory drugs, like ibuprofen (Brufen®) for the muscle cramps and aches
- Paracetamol for headaches
- Diphenoxylate (Lomotil®) for diarrhoea
- Antacid for indigestion
- Diazepam (Valium®), clonazepam (Rivotril®), Oxazepam (Serepax®) or hydroxyzine (Aterax®) for cramps, irritability, dysphoria and anxiety (**Important: Benzodiazepines is BEST AVOIDED and when used, it should be used with great care in opioid use disorders because of the risks of overdose with opioids and partial opioid agonists as well as the risk of co-addiction or cross-addiction**)
- Temazepam, nitrazepam, hydroxyzine (Aterax®), Promethazine (Phenergan®), or Zopiclone for insomnia
- Prochlorperazine (Stemetil®) / Metochlopramide (maxalon®) for nausea and vomiting
- Loperamide (Imodium®) for diarrhoea
- Octreotide (Sandostatin®) for withdrawal-induced nausea and diarrhoea
- Non-medications: hot/cold packs, relaxation, baths, massages, rubbing ointments, music, acupuncture, aromatherapy etc.

2. Suggested guidelines for the use of Naltrexone:

Naltrexone can be used as an aid to relapse prevention for individuals who have successfully detoxified from heroin and other opioids. This is termed naltrexone maintenance or Antagonist-Assisted-Abstinence. Naltrexone works best in maintenance therapy if a nominated responsible carer is identified to supervise consumption (family/friend/GP/outpatient clinic). It is recommended only doctors experienced in treating substance use disorders prescribe naltrexone.

Naltrexone could be considered if:

- The patient is completely opioid free for 5-10 days. This period can be shortened to as little as 72 hours in selected cases. This applies specifically to outpatients who cannot manage a week of being “clean” on their own.
- The patient is willing to take naltrexone (obtain informed consent).

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- The patient does not have severe or active liver or renal problems (typical guidelines suggest liver function tests no greater than 3 times the upper limits of normal and normal bilirubin); 3-6 monthly monitoring of the patient's liver function is recommended.
- The patient is not allergic to naltrexone.

Before taking the first tablet, request the following:

1. Supervised urine test.
2. Obtain liver function test
3. Give a naloxone challenge of 0,4 mg/ml SC. If signs or symptoms of withdrawal appear, the test is positive and no additional naloxone should be administered, and naltrexone should be delayed. If there are no signs or symptoms of withdrawal within 30 minutes, naltrexone tablets can be started.

Treatment regime for oral naltrexone

A maintenance dose of 50 mg (1 tablet) naltrexone daily produces an adequate block to all opioids. It is recommended that patients get into 'a tablet a day' routine, to prevent skipping or forgetting doses, though the following regimes are acceptable:

1. 50 mg daily Monday to Friday, 100 mg on Saturday
2. 100 mg every other day
3. 150 mg every third day
4. 100 mg on Monday & Wednesday & 150 mg on Friday
5. 150 mg Monday & 200 mg on Thursday

Injectable or implant sustained release naltrexone

Sustained release naltrexone implants or injectable depots are currently only available under Section 21 approval from the MCC. Individual applications are assessed and approved if deemed appropriate. Reasons for a sustained release formula include the desire to remain abstinent but inability to do so even after several inpatient rehabilitation admissions, and patients who have poor compliance to naltrexone tablets and no one to supervise administration of the tablets.

Length of treatment

In general, patients need a treatment period of at least 6 months to make the behavioural changes necessary to remain abstinent, but for many this process can take up to 2 years. Some patients may require it only during the initial transitional phase for a brief period. Some patients may require it only during periods of crisis.

Risks:

1. Accidental overdose when naltrexone is stopped and patients relapse to illicit opioids because of reduced tolerance levels.
2. Precipitation of severe opioid withdrawal symptoms (including seizures).
3. The antagonist effect will affect the effect of all opioids, including analgesics. This may be important in a medical or surgical emergency and therefore the use of some form of identification, like a medical alert bracelet is suggested.

3. Suggested Guidelines for Substitution Prescribing:

Aims of substitution prescribing:

- Prevent or reduce withdrawal symptoms from opioids
- Prevent or reduce cravings for opioids
- Prevent relapse to illegal opioid use
- Attempt to restore some of the disrupted physiology of chronic opioid use
- Reduce premature death
- Reduce the spread of blood-borne diseases associated with injectable drug use
- Facilitate psychosocial rehabilitation of those in treatment
- Improve health of individual
- Improve social wellbeing of the individual
- Improved functional ability of the patient
- Reduce level of involvement in crime associated with opioid use
- Improve economic status of the patient
- Reduce use of other drugs
- Not all patients will achieve all these aims. Achieving aims is often a slow process and any improvement should be seen as of value and a step in the right direction.

Recommendations:

- It is recommended that all prescribers be accredited (attend an accreditation course) in substitution prescribing, and that funders only fund such accredited practitioners.
- Patients for substitution treatment should be carefully selected. In young patients or patients with a short history of opioid use or this use of lower potency opioids, an opioid free program might first be tried. However, OST should be considered if it is the patient's choice.
- Patients need to have a diagnosis of opioid dependence and have evidence of physical dependence (tolerance, withdrawal).
- Patients should be well motivated and give informed consent to substitution prescribing.
- Patients should ideally be 18 years or older. It is recommended that a specialist second opinion be obtained before starting patients younger than 18 years on substitution treatment.

Precautions:

- Concomitant medical or mental health problems increase the complexity of management and may even increase risk of overdose and death.
- High-risk poly-drug use, especially drugs that cause sedation like alcohol, anti-depressants or benzodiazepines.
- Alcohol dependence – ensure if methadone liquid is used, that it does not contain alcohol (e.g. Physeptone syrup), especially if concomitant disulfiram is used.
- History of possible reduced tolerance (e.g. after a detox or naltrexone implant)
- Individuals who are at risk of self-harm.

Initial assessment: (See appendix A3 – “assessment of the opioid addict”)

- Consider whether substitution therapy is appropriate. How does the person wish to change, and will substitution therapy encourage this?
- Always perform a urine or saliva test to confirm opioid use. (Before initiating substitution therapy, it is usually best to ensure that at least one positive urine test for opioids was obtained).
- Before commencing OST, it is suggested that all patients be provided with adequate written treatment information, including an understanding that they may experience withdrawal symptoms should they stop the medication without gradual reduction. Signed, informed consent is suggested.

Initiating treatment and stabilization:

- Supervised consumption is required (at least initially, until the patient is stable and the prescribing doctor feels confident that the patient will comply) – see notes, appendix C. If supervised consumption is not possible, buprenorphine-naloxone should be used.
- Drug testing: patients should be tested as often as indicated, at least weekly at first.
 - Positive test: these individuals should be evaluated further. During the initiation and stabilization phase, illicit drug use usually indicates an inadequate dose of substitution medication, and a dose increase should be considered. However, if the client remains disinterested and amotivated to comply, substitution prescribing should be discontinued.
- The introduction of medications that induce or inhibit metabolizing enzymes of substitution medication, e.g. the CYP 3A4 enzyme system, requires careful monitoring and dose adjustment if appropriate.
- Never increase the dose without a practitioner first seeing the person.
- If possible, review the person daily during the first few days in order to titrate the dose against withdrawal symptoms, until the person is clinically stable on their substitution dose. If this is not possible, the person should be seen every 2-3 days and the dose increased only then.
- Methadone should be managed especially for safety during initiation (“start low- go slow”) to guard against dose accumulation early on in treatment and concomitant risk for overdose, whereas Buprenorphine should be managed for comfort (“start low- escalate rapidly”) to avoid precipitated withdrawal as well as inadequate withdrawal suppression and early drop out.

Maintenance phase

- Supervised consumption of methadone and buprenorphine should be continued until patient has been stable for at least 3 months. Careful monitoring and regular follow-up is required, as is regular urine testing and weekly dispensing (at least initially). Care plans should be individualised.
- Once the patient is stabilised on a substitution dose, positive tests should stop. If it happens, it should be investigated and addressed. Furthermore, erratic attendance should be confronted and dealt with (it usually indicates poor compliance). Clinicians should be vigilant about the fact that medication could be diverted to fund illicit drug use. Supervised consumption may need to be refined by breaking oral medication and take-home doses should be restricted in these cases. Sometimes, drug interactions with newly prescribed medication impair the availability of substitution opioid, e.g. CYP3A4 inducers. This is not uncommon as these patients often have comorbid medical and mental

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health problems. Such patients may need dose adjustment. Remember that although zero drug use is the ideal, many patients may occasionally “slip” for short periods and this does not impede their ability to benefit from treatment and can be a valuable learning opportunity for them. Patients with on-going positive drug testing or poor compliance require further assessment and may even need to have a standard detoxification (see above) or may require inpatient treatment.

- Any evidence of diversion of medication should lead to rapid detoxification is required and immediate termination of treatment. Diversion implies selling, trading, sharing or giving away of medication to another person and should be distinguished from non-adherence i.e. taking more or less than prescribed or using medication via a different route.
- A thorough review is indicated every 3 months and should include reassessing the treatment plan with respect to goals achieved and new goals aimed for.
- Psychosocial interventions should be encouraged during treatment, which should include attempts at achieving greater life stability.

Dose reduction and discontinuation of maintenance

- Better long-term outcomes are enhanced by longer treatment periods (1-2 years) and dose reduction should only be attempted when the client is ready and motivated for this (e.g. has a stable and supportive lifestyle). Many patients require however long-term treatment.
- Gradual reductions over weeks result in better outcomes than rapid reductions.
- Patients may require more regular follow-up during the dose-reduction phase. Worsening in the patient’s feelings of wellbeing, or an increase in illicit drug use requires a temporary cessation or slowing down of the dose reduction.
- Dose reductions should be made in consultation with the patient. Continued reductions in a distressed and uncomfortable patient are counter-productive.
- Symptomatic medication (see above) may also be used during dose reduction.
- On-going psychosocial support is necessary and structured aftercare reduces the risk of relapse and supportive care is advised for at least 6 months following cessation.

Some clinical drug interactions to be aware of:

- Buprenorphine and methadone are extensively metabolized by the liver via the CYP 3A4 cytochrome P450 system and methadone also by CYP2D6, and blood levels can be affected by the concurrent use of drugs that either inhibit or induce liver enzymes.
- Drugs that increase blood levels include: (may cause side-effects or in case of methadone, evidence of toxicity)
 - Selective serotonin re-uptake inhibitors (SSRIs) (e.g. sertraline, fluoxetine)
 - Serotonin and noradrenaline re-uptake inhibitors (SNRIs) (e.g. venlafaxine)
 - Broad-spectrum antifungals and anti-bacterials (e.g. clotrimazole)
 - HIV treatments (e.g. zidovudine, ritonavir)
 - Hormones (e.g. progesterone, ethinylestradiol)
 - Calcium-channel blockers (e.g. nifedipine, verapamil)
 - Antibiotics (e.g. erythromycin)
 - Other (quinidine, midazolam, cyclosporin, vinblastine, bromocriptine, cimetidine, grapefruit juice)
- Drugs that decrease blood levels include: (these may cause withdrawal symptoms or illicit opioid use due to inadequate receptor blockade)
 - Anti-epileptics (phenobarbitone, phenytoin, primidone, carbamazepine)
 - Glucocorticoids

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- Anti-tuberculosis medication (rifampicin, rifabutin)
- Certain antiviral drugs (e.g. nelfinavir, ritonavir, efavirenz, nevirapine)
- Practitioners should be aware of these potential drug interactions. They are rarely clinically significant in the buprenorphine-substituted patients, but may have serious implications with methadone.
- Use of monoamine oxidase inhibitors is contra-indicated
- Use of other opioid agonists, e.g. pethidine, is not advised, especially with methadone, due to risk of toxicity
- Opioid antagonists may precipitate withdrawal
- Extreme caution is advised with other CNS depressants, e.g. benzodiazepines, other hypnotics and anxiolytics, alcohol. Avoid prescription of benzodiazepines or benzodiazepine-like substances.

3 (i) Buprenorphine (Subutex®) or Buprenorphine-Naloxone (Suboxone®) substitution prescribing:

See general guidelines above.

Initial assessment:

- Check liver function tests (LFTs) and screen for concomitant liver abnormalities, like Hepatitis B or C and for medication that may affect liver function before starting substitution treatment. These findings need to be taken into consideration when choosing buprenorphine or buprenorphine-naloxone as these patients are at higher risk of accelerated liver problems. Treatment may be started while waiting for the results, providing the patient is well.
 - In people who do not have liver disease, LFTs should be checked regularly, and some experts would advise at least every 6 months.
 - In people with mild alterations of LFTs, but who are well, monitor at least every 6 months (more frequently if clinically indicated) and monitor alcohol intake.
 - In people with symptomatic liver disease (e.g. hepatitis C positive, with alcohol misuse), seek specialist advice. LFTs need to be checked regularly: usually a minimum of every 2-3 months.
 - If there is evidence of a marked deterioration in LFTs, seek specialist advice.
 - Buprenorphine or buprenorphine-naloxone should never be started if the person has evidence of ascites or cirrhosis.

Initiating treatment and stabilization on buprenorphine or buprenorphine-naloxone:

- Withdrawal symptoms may be precipitated by the partial antagonist properties of buprenorphine. These typically occur 30 minutes - 3 hours after the initial dose of buprenorphine and should be suspected if withdrawal significantly worsens within this time after taking the first dose. To avoid withdrawal when switching from heroin, delay the first dose of buprenorphine or buprenorphine-naloxone until clear clinical evidence of opioid withdrawal (wait at least 8 hours after the last dose of heroin). (The clinician could ask the patient to not use any opioids after 10 pm the previous night and come to the surgery the following morning, when they are in active withdrawal. Examine to ensure patient is in established opioid withdrawal before giving first dose of medication; a rating scale may be useful to confirm this. In a reliable patient, the patient can be advised to wait until they are clearly in withdrawal and very uncomfortable, before taking the first tablet).
- If the person experiences severe precipitated withdrawal symptoms:

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- Further increases in buprenorphine are not advisable.
- Symptomatic treatment and Clonidine can be given (see above).
- The usual recommended starting dose is 2- 4 mg or 2/0.5mg to 4/1mg. Most patients will require 4 mg or 4/1mg. When starting buprenorphine or buprenorphine-naloxone, start low and titrate rapidly providing there are no problems.
 - Use caution in patients who are using alcohol, other opioids (for chronic pain) and sedating drugs; or have comorbid medical conditions (e.g. severe respiratory, renal, or hepatic disease)
 - Caution in patients who take a long-acting opioid like methadone- increased risk of precipitated withdrawal.
- Further doses of 2-4 mg or 2/0.5 – 4/1mg can be given every 2-4 hours (as peak plasma levels are only reached after 2-4 hours) until the patient is comfortable and not experiencing objective withdrawal. Ideally patients should be observed after each dose to ensure they are not overly sedated, but where this is not possible, the prescriber should be telephonically available to discuss adequate dosing. Maximum registered dose in South Africa is 16mg or 16/4mg.
- Prescriptions may be given as fixed, increased doses (e.g. 4mg+4mg day 1; 12mg day 2 and 16mg day 3); or a flexible regime allowing some control by the patient, may also be used.
- The total dose used on day one can then be repeated the next day and increased further by 2-4 mg or 2/0.5 – 4/1mg daily (usually 4 mg for severe withdrawal) according to clinical response over the next few days, up to a maximum of 16 mg or 16/4 mg (the maximum registered dose). Some patients may require higher doses, up to 32mg.
- The ideal dose is one where there is no withdrawal symptoms, no cravings and where the use of any illicit opioid does not have any effect/only minimal effect.
- Although some prescribers use buprenorphine as a twice-daily dose, it has a long half-life and once daily dosing is usually as effective and a simpler treatment regime to comply with.

Maintenance phase with buprenorphine or buprenorphine-naloxone:

- The average daily maintenance substitution dose of buprenorphine is between 8 and 16 mg or 8/2 mg and 16/4 mg of Buprenorphine-Naloxone. 16mg or 16/4mg is the maximum registered dose in RSA. Some international guidelines recommend a maintenance dose of between 12-24 mg/day. Some patients require higher doses up to 32 mg.
- Buprenorphine is usually prescribed for daily use; alternate-day dosing is occasionally used in some individuals where consumption of all doses is supervised; it should not be considered until the person has been stable for at least 3 months. The effectiveness of alternate-day dosing may suit only 30-60% of people and should be considered only after consultation with an experienced prescriber. Less than daily dosing is useful in patients in whom on-going supervised consumption is indicated. The dose should be titrated to clinical need, and the following is a guide only:
 - Two-day regimen: twice the daily dose on alternate days, up to a maximum of 32 mg per dose (off-label use as the maximum registered daily dose is 16 mg per day).
 - Three-day regimen: three times the daily dose every third day, up to a maximum of 32 mg.

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- People who have been stable on buprenorphine for 3 months, require daily supervision and who have no high-risk drug use may be considered for reduced-frequency dosing.

Dose reduction and discontinuation of maintenance buprenorphine or buprenorphine-naloxone:

- Dose reductions are best negotiated with the patient. The speed of reduction is determined by the patient's motivation to reduce the dose and by the level of discomfort experienced during the withdrawal process. It is advised to withdraw at the level that the patient feel comfortable with.
- As a rough guide: (use equivalents of buprenorphine-naloxone if this is used):
 - For doses above 16 mg, reduce by 4 mg per week or fortnight
 - For doses of 8-16 mg, reduce by 2-4 mg per week or fortnight
 - For doses of < 8 mg, reduce by 2 mg per week or fortnight
- Many patients do not tolerate this suggested dose reduction regime and require slower down-titration –when reducing the dose is poorly tolerated, down-titration even be can be done as slow as by reducing by 1mg (half 2mg tablet) at a time, and this can even be reduced slower due to Buprenorphine's very long half-life, by taking the reduced dose alternative days initially.

3(ii) Methadone substitution prescribing:

See general guidelines.

Methadone is available as a cough syrup, called Physeptone syrup®, at a concentration of 2 mg/5 ml, that is not registered or suitable for long-term OST and as Equity methadone, at a concentration of 2mg/ml, which is registered and suitable for OST. Although this formulation has a thickening agent to deter injecting use, there have been reported cases of intravenous use, which increase the overdose death risk. Furthermore, methadone has street value, making black market diversion a risk and therefore supervision of consumption is indicated for all patients, with cautious and carefully monitored introduction of take-home doses, when patient has achieved stable recovery.

Contraindications for methadone substitution prescribing:

- Severe liver impairment (methadone may precipitate hepatic encephalopathy)
- Severe respiratory depression, acute asthma
- Acute alcoholism
- Head injury or raised intracranial pressure
- Ulcerative colitis, biliary or renal tract spasm
- Use of monoamine oxidase inhibitors or within 14 days of stopping this

Dangers of methadone substitution:

- Methadone poisoning - risk increased with low opioid tolerance, too high an initial dose, too rapid dose increase, drug interactions or slow methadone clearance
- Accidental overdose – risk increased by concurrent use of CNS suppressant drugs
- Poisoning of someone other than the patient
- Illegal diversion and trafficking of methadone

- In order to minimise/avoid these dangers, the strict guidelines provided here, should be followed, including careful and slow up-titration of the dose, ongoing regular monitoring of the patient and supervised consumption.

Initial assessment:

- See general guidelines above

Methadone may increase the QT interval and this risk is increased with higher doses, concomitant use of a P₄₅₀ 3A4 inhibitor, hypokalaemia, cardiac abnormalities, low serum magnesium, concomitant use of drugs that cause electrolyte abnormalities or drugs with the potential to prolong the QT interval and impaired hepatic function. The following recommendations thus apply:

- Inform patients of arrhythmia risk with methadone
- Clinicians to assess for structural heart disease and history of arrhythmia and syncope.
- Obtain a pre-treatment ECG to measure QTc interval and a 30-day follow-up ECG.
- Obtain additional ECG's annually, if doses exceeding 100mg are used, or in cases of unexplained syncope or seizures.
- Clinicians should be aware of interactions between methadone and other drugs that prolong QTc, as well as drugs that decrease the elimination of methadone.
 - If QTc > 500ms: discontinue methadone or reduce dose, eliminate contributing factors like hypokalaemia etc.
 - If QTc 450-500ms: discuss risks and benefits with patient, eliminate contributing factors and monitor more regularly

Initiating treatment (usually first 2 weeks of treatment)

- It is important to achieve a balance between adequate relief of withdrawal symptoms and avoidance of toxicity, sedation and even death. Inadequate doses may lead to “topping up” with heroin, benzodiazepines or other opioids, with potentially lethal consequences.
- **It is very strongly advised that all methadone doses should be supervised, at least initially.** Identify a person who will supervise consumption on a daily basis before initiating treatment. A professional person, like a pharmacist or practice nurse is the best option. Many pharmacies are willing to act as supervisors and pharmaceutical companies are mostly willing to train them. The patient should be asked to speak after dosing to ensure that they have swallowed their medication. Although a responsible other person, e.g. a family member can be used for this purpose, this is not ideal. (Non-professional supervisors do not have the clinical skills to diagnose evidence of subtle intoxication/withdrawal and patients are often very skilled at manipulating relatives. There is also a risk that medication can be used as leverage by the supervisor to get a patient to do things for the supervisor, allowing for a risk of medication doses to be missed. Furthermore, secure storage for the medication is essential.) An unbiased and objective supervisor is thus the ideal.
- The first dose of methadone should be determined for each patient based on the level of tolerance obtained through the history (including the quantity, route, frequency, money spent etc.). A definite period of observation for objective signs of withdrawal may also be helpful.
- This first dose is usually between 10 and 30 mg, but may be lower. A dose of 20 mg for a healthy, young 70 kg patient can be presumed safe in most cases. Starting doses should

never exceed 30 mg unless a clinician experienced in the treatment of opioid use disorders deems it necessary.

- Patients should ideally be observed for 3-4 hours after the first dose for signs of toxicity or withdrawal. If facilities for observation are not available, patients and their family/friends should be informed to report any evidence of sedation immediately and seek urgent help if with any impaired consciousness. If any health concerns are present, patients can also be admitted in order to start methadone treatment.
- If the patient experiences persistent withdrawal symptoms as observed by a clinician experienced in the treatment of opioid disorders at 4 hours, and is in a supervised environment, a supplementary dose of 5 mg methadone may be considered. The maximum dose for the first day should not exceed 40mg.
- The ideal initiation dose is a dose that causes suppression of withdrawal during peak levels (2-4 hours after ingestion), without causing sedation or evidence of intoxication and the patient should be warned that they should expect to feel uncomfortable as the medication begins to wear off and the time for the next dose approaches. This will gradually improve over the next few days, as the methadone accumulates in the body and steady-state is achieved and with gradual dose increases. If the patient did not have significant withdrawal symptoms during the first 12 hours after dosing during the induction phase, they usually need more time on the same dose, while the drug accumulates in the body (usually 3-5 days).
- Patients should ideally be followed up daily during the induction phase. The ideal time for a follow-up appointment is about 2-6 hours after dosing. If this is not possible, the clinician should see the patient at least every 3-4 days and should be available telephonically for any problems or queries. Provide emotional support and cautiously titrate the dose against withdrawal symptoms, until the person is clinically stable on their initiation dose. This may be done by **cautiously up-titrating** by up to 5mg every 3-4 days. The dose should never be increased without seeing the patient. Up-titration should continue until withdrawal symptoms are eliminated and cravings stop, but at a rate that prevents sedation or overdose. Patients should be on the same dose for 3-4 consecutive days, before any dose adjustment can be considered. Maximum dose at the end of 1st week should not exceed 40 mg.
- With daily dosing, a significant proportion of the medication remains in the person's system and gradually accumulates. A dose that is barely adequate on day 1, may be cause sedation and overdose by day 5 as serum levels will continue to increase for about 5 days after any dose change. It takes 4-5 half-lives (there is considerable variation in methadone's $t_{1/2}$ from about 20-36 hours) for the drug to reach steady state. During this initiation phase, accumulation of methadone is a big risk.
- There is a significantly **risk for overdose** in the first 14 days due to accumulation in the body. Concomitant use of sedatives increases this risk and should be avoided. One study found a 5x-increased risk for death with concomitant benzodiazepine use. Patients should be warned to avoid alcohol and over-the-counter sedating medication, as this may also contribute to death. Patients often pressurise prescribers for hypnotics, but patients should be informed of risks, reassured that they will feel better within a few days and hypnotics (even non-benzodiazepine hypnotics, sedating anti-depressants, anti-histamines, or anti-psychotics) should be avoided.
- Patients should be warned to avoid driving or using heavy machinery until they are fully stabilised, particularly in the first few hours after dosing. The ideal time to take medication is in the morning, because the overdose risk may increase during the night. Educate patients and their families or significant others of the risk of overdose, signs of a

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possible overdose and a plan to manage this, should it occur. Provide the written advice and instructions in this regard to the patient.

- Extra caution should be taken if patient has low tolerance, respiratory illness, in elderly patients or young children and patients on medication that inhibits methadone metabolism, like certain SSRI's, macrolide antibiotics, fluconazole, quinolones, cimetidine and certain anti-retroviral medications.
- During first 2 weeks of opioid treatment, there is a significantly increased risk of death and the clinician needs to balance minimising this risk, with prescribing an effective dose that is sufficiently appropriate to the patient's needs, in order to retain them in treatment and prevent harm from illicit use. Patients should be informed that they could expect discomfort in these first 2 weeks.
- **Missed doses** during initiation phase: If patient misses 2 or more doses, titration should start from initial dose (10-30mg) for at least 3 days.

Stabilisation on methadone

- The aim of the stabilization phase is to determine a dose that allows the patient to stabilise without oscillating between intoxication and withdrawal. Following ingestion, methadone levels usually peak at about 2-4 hours after ingestion and then slowly begin to drop. At the right dose, this peak is not associated with intoxication. At steady state, the trough levels are such that there is sufficient effective therapeutic opioid effect for the patient to remain comfortable. The result is that the individual feels "normal" throughout the dosing interval. Patients should be aware that it would take a while for them to safely achieve this steady state.
- During this phase, patients often only experience partial relief and often continue to use opioids. Continue **to see at least weekly and gradually increase** by 5 mg/ week until cravings stop and withdrawal symptoms are eliminated, urine drug screens become negative, at a rate that prevents sedation or overdose. Document reasons for dose adjustment and never increase a dose without seeing the patient. The stabilisation phase ends when the patient has been on a stable dose for 1 week, without withdrawal symptoms, significant cravings and illicit opioid use.
- **Drug screens** are an effective aid in treatment. Self-report about active drug use is generally very accurate, but patients tend to under-report drug use. Refusal or poor co-operation with drug testing should be viewed as positive drug use until proven otherwise. Ideally urine should be collected under supervision and testing should be done weekly initially and once a patient has been stable for 6 months, this may be reduced. Random testing later in treatment is adequate. Any suggestions of a lapse should be accompanied by increased testing.
- If there is an inconsistent history of withdrawal or one isolated symptom (like insomnia, abdominal discomfort) or withdrawal is not related to a time of the dose, alternative explanations for this should be sought. A dose may be considered acceptable if the patient sleeps comfortably at night and has only mild discomfort on awakening. If insomnia is not accompanied by other symptoms of withdrawal and does not improve on dose increase, consider other causes for this, like anxiety, depression, use of alcohol or stimulants, daytime napping or day-night reversal. Benzodiazepines should be avoided. The Drug and Alcohol Services of South Australia website provides an "insomnia management kit" for GP's that can help in this regard. (<http://www.dassa.sa.gov.au/site/page.cfm?u=451>)
- The optimum dose is one that is effective throughout the day and night, without causing sedation. After stabilisation, the most common cause for overdose is drug-drug interactions and patients should be warned to disclose methadone use to any medical

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practitioner or pharmacist and to inform the treating doctor if another practitioner prescribes any new medication. Overdose may also result from discontinuation of medications that promote methadone metabolism, like carbamazepine or phenytoin.

Maintenance phase

- Once a dose is reached where the desired therapeutic effects are achieved (i.e. no illicit use, withdrawal or cravings), the maintenance phase begins and continues until there is a reason to alter the regime. During this phase, patients are largely tolerant to methadone. Patients may occasionally ask for dose increases due to re-emerging subjective withdrawal, cravings or relapse. Higher doses of methadone (>60mg) have been shown to be more effective than low doses and many patients require doses of between 80 and 120mg. **Dose adjustments** may be made by 5mg every 1-2 weeks if needed. ECG monitoring is required at doses above 100mg.
- **Missed doses** indicate a variety of problems and should be addressed. Pharmacists should inform the clinician of this. If the client has missed one or 2 days, they may receive their usual dose, providing they are not intoxicated. If they miss 3 consecutive days, they may have a clinically significant loss of tolerance and the patient need evaluation before they could receive further medication. These patients may be prescribed 50% their usual dose and once they show tolerance to this dose, it may be gradually increased again. The patient should be assessed before every dose increase and this should be no faster than 10mg/2 to 3 days. With 4 or more missed days, the safest course of action is to restart at 30mg or less and increasing every 2-3 days by up to 10mg/time.
- If a patient reports **vomiting medication**, doses are not replaced unless a health care practitioner has observed this. Address the cause of emesis. If it occurs less than 15 minutes after dosing, replace 50-75% of dose. If 15-30minutes, replace 25-50% and if >30 minutes, do not replace.
- If patient has **not responded** at a dose of 120mg, discuss with an expert in the treatment of opioid dependence. Doses should not be increased unless there is consistent cluster of withdrawal symptoms that occur at a predictable time, at the end of the dosing interval. Cravings are not enough reason for dose increases at levels above 120mg. Enquire about cognitive symptoms, like sedation, tiredness or poor memory and concentration. Some patients report an improvement in energy levels, if high doses are slowly and cautiously tapered by 20-40 mg.
- Some patients have a rapid metabolism and are drowsy shortly after dosing, but experience withdrawal before the next dose. This is often a problem during the 3rd trimester of pregnancy or if medications are used that increase metabolism (like HIV drugs). These patients may benefit from flattening of the peak-trough effect, by dividing their doses. Chronic pain may be another indication **for splitting doses**. Split doses should not be considered if patients are still clinically unstable and do not qualify for take home doses.
- Patients are able to remain on this dose for years without dose increases. Dose reductions or discontinuation are associated with high rates of relapse and many patients require this treatment indefinitely. Treatment should be continued as long as the patient benefits from treatment and wishes to continue and suffers no ill effects as a result of it.
- During the maintenance phase, the clinician should continue weekly **follow-up** with supervised consumption. Patients need to be seen at least once every 1-2 weeks for the first year, depending on the response. As the patient begins to stabilise their lifestyle, they find daily-supervised consumption extremely tedious. Once the patient has managed to achieve a stable home-condition, becomes productive, has resolved legal problems and is

compliant with treatment and clean from illicit drugs, they may be considered for take-home doses.

- Studies have found that **take home doses** is an effective contingent for reducing opioids, cocaine and benzodiazepines and a less restrictive take home policy has better retention rates. However, methadone diversion is common and diverted methadone is the main cause of methadone deaths. Patients who have been clinically stable for *at least 3 months* and who are able to safely store methadone in a locked cupboard, may be considered for take-home doses. The benefit of take home doses needs to be weighed up against the safety risks. One take home dose can be considered for a patient stable for 3 months, if all goes well, this may be increased by 1 take home /week for every additional month the patient does well, up to a maximum of one week's worth of medication (6 take home doses). This should be re-assessed and visits increased if the patient becomes unstable, takes medication early or reports lost or stolen medication. Patients may be asked to return empty containers to reduce risk of diversion. Take home privileges should be stopped if there is diversion of methadone or tampering with urine specimens. There is risk that if patients have diverted all or part of their medication, there may be a reduced level of tolerance and the dose dispensed may need to be reduced by 50-75% and the patient assessed for evidence of withdrawal.
- Patients who appear to be **intoxicated** should not be medicated, until they have seen a doctor who is sure that they are unaffected.
- A thorough review is indicated every 3 months and should include reassessing the treatment plan with respect to goals achieved and new goals aimed for. Psychosocial interventions should be encouraged during treatment. This should include attempts at achieving greater stability in all areas of function.

Dose reduction and discontinuation of methadone:

- Better outcomes are enhanced by longer treatment periods (1-2 years) and dose reduction should only be attempted when the client is ready and motivated for this (e.g. has stable and supportive lifestyle). Do not attempt to taper if there are untreated comorbid mental health problems or poor social support
- Gradual reduction over weeks results in better outcomes than rapid reduction. Patients may require more regular follow-up during the dose-reduction phase. Worsening in the patient's feelings of wellbeing, or an increase in illicit drug use requires a temporary cessation or slowing down of the dose reduction.
- Reduce dose by 5-10 mg/week to a level of 40 mg and then by 5 mg/week. Dose reductions can also be slower if clinically indicated. Negotiate each reduction with the patient and do not make changes more frequently than once per week. Continued reductions in a distressed and uncomfortable patient are counter-productive. Tapering should be gradual and comfortable for the patient and may last from 2 weeks to 6 months on an outpatient basis.
- Signs and symptoms of withdrawal will begin to rise as the methadone dose falls below 20 mg/day. Peak symptoms occur 2-3 days after cessation and may be slow to subside (up to 10-20 days). Patients can be transferred onto buprenorphine with doses of 30 mg or lower.
- When a dose of 10mg is reached, symptomatic medication (see above) may also be used during dose reduction.
- Ongoing psychosocial support is necessary and structured aftercare reduces the risk of relapse and supportive care is advised for at least 6 months following cessation.

From "Clinical guidelines and procedures for the Use of Methadone in the Maintenance Treatment of Opioid Dependence" Australian Government Drug Strategy, Aug 2003; Equity methadone Guidelines for Maintenance treatment for opioid dependence.

4. Guidelines for transferring a patient from methadone to buprenorphine or buprenorphine-naloxone:

- Patients can be transferred from high dose methadone to buprenorphine, but this requires expertise and sometimes, inpatient care, especially during pregnancy. Consult an expert in the field.
- Reduce the dose of methadone as low as possible (preferable below 30 mg).
- Cease methadone and commence buprenorphine or buprenorphine-naloxone > 24 hours after the last methadone dose – wait for objective signs of early withdrawal (an objective withdrawal rating scale may be useful, see appendix D)
- The likelihood of precipitated withdrawal is reduced as the interval between last dose of methadone and first dose of buprenorphine or buprenorphine-naloxone increases.

Last dose of methadone (mg)	First dose Buprenorphine (mg)	Day 2 dose of buprenorphine (mg)
20-40	4	6-8
10-20	4	4-8
1-10	2	4

- For buprenorphine-naloxone, use equivalent doses to the buprenorphine dose, i.e. 4mg buprenorphine compares with 4/1mg of buprenorphine-naloxone; 8mg of buprenorphine compares to 8/2mg of buprenorphine-naloxone.
- Communication between prescriber, dispensing staff and client is important. Regular review, preferable daily, for the first few days is advisable.
- Clients may expect to feel uncomfortable for several days (up to 2 weeks) after transfer, and require frequent reviews and added support.
- Increase dose only after reviewing the clients and consider increments of 2-4 mg at a time if needed.

5. Guidelines for transferring a patient from buprenorphine to buprenorphine-naloxone:

- This transition can be made by simply changing the patient to the corresponding equivalent dose. Example: if a patient is taking 16mg of buprenorphine, he or she could simply be swapped to 16/4mg of buprenorphine-naloxone.

6. Guidelines for transferring a patient from Buprenorphine or Buprenorphine-Naloxone to methadone

- It is suggested that the daily dose of buprenorphine be reduced to 16mg or less for several days before transferring a patient onto methadone.
- Methadone is commenced 24 hours after the last dose of buprenorphine.
- Induction from buprenorphine onto methadone is similar than from other opioids and the rule “start slow go-slow” applies, i.e. a starting dose of less than 30mg is suggested. It is suggested that the starting dose be determined by observing the patient’s clinical response, and keeping in mind buprenorphine’s long half-life.
- Lower doses of buprenorphine require lower doses of methadone.
- Care should be taken to not increase methadone too quickly.

Appendix C:

Information for prescribing opioid controlled drugs
Notes on supervised consumption

Information for prescribing opioid controlled drugs:

- Legally, a pharmacist cannot dispense opioid substitute, controlled drugs unless the following information is included on the prescription:
 - The person's name and address
 - The form and strength of the preparation
 - The total quantity of the preparation or the number of dose units, in both words AND figures
 - The dose
 - The signature of the prescriber who has written the prescription
 - The date of signing by the prescriber who has written the prescription
- State the date when it is intended that the first instalment should start.
- Specify the interval (e.g. daily dispensing) and the amount required or instalment dispensing on the prescription.
- If the prescriber wants supervised consumption, specify 'supervised consumption' on the prescription if a local scheme is in place.
- The maximum amount of a controlled drug that can be dispensed on a single prescription should be limited to a supply sufficient to last 28 days.
- A prescription for a controlled drug is valid for 28 days from the date stated thereon.
- Where possible, always issue a prescription directly to the drug user. A copy of the prescription may also be faxed to the pharmacy to prevent tampering with the prescription.

Notes on supervised consumption:

- Supervised consumption is advisable initially in all patients.
- Following initiation, patients on buprenorphine-naloxone do not require supervised consumption.
- Take home doses of methadone should only be considered in exceptional cases of patients who have been stable for extended periods.
- Supervisors should ideally be a professional person and may include:
 - The medical practitioner or a practice nurse. (Dispensing licence required by law for dispensing. Alternatively the medication could be dispensed by a pharmacist to the doctor's surgery and consumption supervised by the practice nurse or medication practitioner)
 - A local arrangement may be negotiated with a pharmacist for supervised consumption.
 - If no professional person can be identified a responsible adult, who may be a family member, should keep the medication safe and supervise consumption. (This is *not* an ideal arrangement as it may lead to conflict within families and may increase the chance of diversion)
- Take home doses of medication act as a reward for good compliance with the treatment plan. It should not be prescribed if the person shows a continued and unstable or unauthorized pattern of drug misuse. The person should then attend the

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Practice, Clinic or pharmacist on a daily basis for supervised consumption until stable. Pro's and con's of take home doses should be weighed up for each patient.

- Benefits of take home doses:
 - Improves reintegration into community
 - Promotes responsibility of client
 - Reduces travel and dispensing costs and inconvenience
- Concerns of take home doses:
 - Increased overdose risk
 - Risk of diversion
 - Risk of injecting buprenorphine or methadone
 - Risk of poor publicity about substitution prescribing.
- If the client has been entrusted with taking the substitute drug unsupervised, initially no more than one week's supply should be dispensed at one time.

Appendix D:

Rating scales for withdrawal symptoms:

Opioid dependent patients are often poorly skilled at self-soothing their agonising cravings and managing their negative emotional states and tend to focus on immediate chemical relief as the only viable option to manage any distress. They are also often very skilled at conveying subjective discomfort to others, including health care providers. The prescriber, who is not used to dealing with addicts, tends to interpret these demands for urgent relief as withdrawal symptoms and tends to respond by providing medication. A withdrawal rating scale is therefore invaluable in determining the degree of withdrawal that a patient is experiencing.

Objective opioid withdrawal scale: (OOWS):

Observe patient unobtrusively during a 5-minute observation period. Then indicate a score for each sign and add scores to obtain a total score.

	Sign	Measures		score
1	Yawning	0= no yawns	1=or more yawn	
2	Rhinorrhoea (runny nose)	0<3 sniffs	1=3 or more sniffs	
3	Piloerection (goose flesh) – observe arm	0=absent	1=present	
4	Perspiration (sweating)	0=absent	1=present	
5	Lacrimation (tearing)	0=absent	1=present	
6	Tremor (hands)	0=absent	1=present	
7	Mydriasis (pupil dilatation)	0=absent	1=>3mm	
8	Hot and cold flushes	0=absent	1= shivering /huddling for warmth	
9	Restlessness	0=absent	1=frequently shifts position	
10	Vomiting	0=absent	1=present	
11	Muscle twitches	0=absent	1=present	
12	Abdominal cramps	0=absent	1=holding stomach	
13	Anxiety	0=absent	1= mild to severe	
Total score				

Range 0-13 Score :

Reference: Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987) Two New Rating Scales for Opiate Withdrawal, American Journal of Alcohol Abuse, 13, 293-308

2. Clinical Opiate Withdrawal Scale (COWS)

For each item, circle the number that best describes the patient's signs or symptoms. Rate just on the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Patient Name: _____		Date: _____	Time: _____
1. Resting pulse rate: _____ beats/minute Measured after the patient is sitting or lying for one minute. 0 Pulse rate 80 or below 1 Pulse rate –100 2 Pulse rate –120 4 Pulse rate greater than 120		7. GI upset: over last half hour 0 No GI symptoms 1 Stomach cramps 2 Nausea or loose stool 3 Vomiting or diarrhoea 5 Multiple episodes of diarrhoea or vomiting	
2. Sweating: over past half hour not accounted for by room temperature of patient activity 0 No reports of chills or flushing 1 Subjective reports of chills or flushing 2 Flushed or observable moisture on face 3 Beads of sweat on brow or face 4 Sweat streaming off face		8. Tremor: observation of outstretched hands 0 No tremor 1 Tremor can be felt, but not observed 2 Slight tremor observable 4 Gross tremor or muscle twitching	
3. Restlessness: observation during assessment 0 Able to sit still 1 Reports difficulty sitting still, but is able to do so 3 Frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds		9. Yawning: observation during assessment 0 No yawning 1 Yawning once or twice during assessment 2 Yawning three or more times during assessment 4 Yawning several times/minute	
4. Pupil size 0 Pupils pinned or normal size for room light 1 Pupils possibly larger than normal for room light 2 Pupils moderately dilated 3 Pupils so dilated that only the rim of the iris is visible		10. Anxiety or irritability 0 None 1 Patient reports increasing irritability or anxiousness 2 Patient obviously irritable, anxious 4 Patient so irritable or anxious that participation in the assessment is difficult	
5. Bone or joint aches: if patient was having pain previously, only the additional component attributed to opiate withdrawal is scored. 0 Not present 1 Mild diffuse discomfort 2 Patient reports severe diffuse aching of joints/muscles 4 Patient is rubbing joints or muscles and is unable to sit still because of discomfort		11. Gooseflesh skin 0 Skin is smooth 3 Piloerection of skin can be felt or hairs standing up on arms 5 Prominent piloerection	
6. Runny nose or tearing: not accounted for by cold symptoms or allergies 0 Not present 1 Nasal stuffiness or unusually moist eyes 2 Nose running or tearing 4 Nose constantly running or tears streaming down cheeks		Total Score: _____ [The total score is the sum of all 11 items.] Initials of person completing assessment: _____	
Score: 5-12=Mild; 13-24=Moderate; 25-36=Moderately severe; >36=Severe withdrawal			

Reference: Wesson DR; Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs 2003; 35(2): 253-259.