South African Guidelines for the management of Opioid use disorders (Part 1)

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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 is 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 it 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 annum[11] 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 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
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 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 use[19] 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 commented. 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 P_{450} 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, nevaripine, 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 (Vivitrol®) 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 stopped[15]; 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 methadone[32], 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 buprenorphine[33] or buprenorphine/naloxone,[34] 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 that 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:
http://www.saams.co.za/Content/Documents/South_African_Guidelines_for_the_Management_of_Opioid_use_disorders_2015.pdf