South African Guidelines for the management of Opioid use disorders (Part 3)

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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.

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 Appendix D: http://www.saams.co.za/Content/Documents/South_African_Guidelines_for_the_Management_of_Opioid_use_disorders_2015.pdf)*

2. Signs and symptoms of opioid withdrawal:

SYMPTOMS	SIGNS
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:

Drug	Time to withdrawal	Peak	Duration
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 port 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.
- 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)
- 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).
- 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.