South African Guidelines for the management of Opioid use disorders (Part 2)

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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.

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 disordere 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 used 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 methadone[43] 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 morbidity[50] (including HIV risk,[51] incarceration[52], and other substance use[53]), mortality[54] 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 that 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: http://www.saams.co.za/Content/Documents/South_African_Guidelines_for_the_Management_of_Opioid_use_disorders_2015.pdf)

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

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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