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Management of Opioid Dependence

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About the Expert

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This publication presents an overview of opioid dependence and its diagnosis and treatment. The pharmacological approaches to the treatment of opioid dependence are managed withdrawal and substitution treatment.[1] Opioid withdrawal is not generally associated with successful long-term outcomes, as relapse after opioid withdrawal is frequent.[1,2] Also, a single detoxification episode should not be promoted as effective treatment.[1] Therefore, the focus of this publication in terms of treatment is on opioid substitution treatment (OST).

In almost all cases, specialist services are the entry point for patients requiring OST. Once stabilised, patients can be transferred to a primary care provider for ongoing OST. GPs can prescribe OST medication on authority from a specialist service. Pharmacists who dispense OST medication also play an important role in supporting the community-based management of patients receiving OST.

The target audience for this publication is psychiatrists, pain management specialists, GPs, and pharmacists with an interest in addiction and its treatment.

Definition and classification

Opioid dependence does not develop without a period of regular use.[1] However, regular use alone is not sufficient to induce dependence.

Opioid dependence is characterised by a collection of cognitive, behavioural and physiological features that develop after repeated opioid use.[1] The International Classification of Diseases, 10th edition (ICD-10) defines opioid dependence as the presence of ≥3 of the following features present simultaneously at any one time in the same 12-month period:

- A strong desire or sense of compulsion to take opioids;
- Difficulties in controlling opioid use;
- A physiological withdrawal state;
- Tolerance;
- Progressive neglect of alternative pleasures or interests because of opioid use;
- Persisting with opioid use despite clear evidence of overtly harmful consequences.

Although intravenous injection is the most common method of opioid drug administration,[2] intravenous use is not included in the ICD-10 diagnostic criteria. Increasingly, people are presenting with oral consumption only resulting in dependence.

Prevalence and burden of opioid dependence

Data from national drug surveys on recreational drug use conducted between 1996 and 2010 in New Zealand suggest that levels of opioid use have remained constant over this period, with <1% of those surveyed reporting current use.[2]

The number of people in New Zealand with opioid dependence was estimated to be 9,953 (95% CI: 8,940–10,967) in a 2008 survey.[3,4] Half of these regular opioid users (n=4608) were not receiving OST;[4] hence, the researchers suggested that the results indicated a substantial level of unmet need.

There is also a risk of becoming dependent on opioids through their prescribed use for chronic pain conditions. In the US, the use of long-term opioid therapy for chronic non-cancer pain has increased dramatically over the past 10–20 years.[5,6] This trend has been attributed to a cultural shift in the prescribing habits of physicians from being opioid phobic to prescribing opioids liberally as well as the availability of certain new formulations of opioids, such as controlled-release oxycodone (OxyContin).[5] Consequently, there has been a steady increase in the number of patients being treated with opioids. As prescription opioid use has escalated so has opioid abuse.

There is evidence that prescription opioid abuse is a problem in New Zealand. A 2010 cross-sectional survey of New Zealand GPs (n=300) revealed that 66% of respondents had diagnosed ≥1 patient with prescription drug misuse problem in the previous year.[7] The most problematic drug classes were opioids and benzodiazepines.

Burden of opioid dependence

International studies indicate that opioid dependence has a significant cost to society.[1] The main cost drivers are utilisation of healthcare services (treatment and prevention), lost productivity (unemployment, homelessness, family disruption), and criminal activities. Studies in developed countries suggest that the economic cost of opioid dependency is 0.2–2% of a country's GDP.

In New Zealand, the community cost (through criminal activity) of untreated opioid dependence is considerable, indicating the importance of treating opioid dependence.[8] According to the results of a local cost-effectiveness analysis, reducing barriers to accessing OST would improve treatment of hepatitis C for injecting drug users on methadone maintenance therapy.[9]

Risk factors for opioid abuse

The Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, defines opioid abuse (opioid use disorder) as a problematic pattern of opioid use leading to clinically significant impairment or distress.[10] It is characterised by the compulsive use of opioids despite adverse consequences from continued use and the development of a withdrawal syndrome when opioid use stops. The adverse consequences include social or interpersonal problems caused or exacerbated by the effects of opioids and forgoing important occupational, social, and recreational activities due to opioid use.

Determinants of opioid abuse primarily rest with the user.[6] Specific risk factors commonly cited in the literature as being associated with opioid abuse include:[5,6]

- Family history of substance abuse.
- Personal history of substance abuse.
- Genetic markers for potential opioid abuse.
- Young age.
- History of criminal activity and/or legal problems, including drink driving.
- Regular contact with high-risk people or high-risk environments.
- Problems with past employers, family members, and friends.
- Risk-taking or thrill-seeking behaviour.
- Heavy tobacco use.
- History of severe depression or anxiety.
- Psychosocial stressors.
- Prior drug and/or alcohol rehabilitation.
- Access to, or prescribing of, opioid medications for chronic pain.

It is unlikely that one of these factors by itself will increase the likelihood of drug abuse in a given individual.[5] The risk is likely to be greatest when risk factors in the psychosocial, drug-related, and genetic categories occur in the same person.

Signs of prescription opioid dependency

Patients with chronic pain who are prescribed opioids are at the greatest risk for misuse of opioids.[6] Typical signs of opioid dependency in chronic pain patients include:[1,2]

- Taking rapidly escalating doses of opioids.
- Taking opioids in greater quantities than prescribed resulting in intoxication or overdose.
- Signs of aberrant behaviour related to opioid medication use, including injecting or snorting oral formulations, recurrent prescription losses, and early pick-up of supply.
- Repeated failure of opioid tapering.
- History of psychological and/or substance use disorders.
- Aggressive or intimidating behaviour.
- Feedback from pharmacies about problem behaviour.
- Other features that raise suspicions of misuse but which are denied.

Patients with chronic pain and patterns of prescribed opioids use consistent with dependence (i.e. more than just tolerance and withdrawal) are candidates for referral to OST service providers.[1,2]

Risk assessment tools

An important component in the management of chronic pain is the ability of the clinician to identify patients most at risk of developing opioid abuse.[5,6] Guidelines for the use of opioids in patients with chronic pain emphasise the importance of opioid risk assessment before commencing long-term opioid therapy.

Commonly recommended tools include the Screener and Opioid Assessment for Patients with Pain (Revised), the Opioid Risk Tool, and the Screening Instrument for Substance Abuse Potential and Screening Tool for Abuse.[5,6] For example, the developers of the Screening Tool for Abuse identified six clinical criteria to predict opioid abuse by patients with chronic pain:[11]

- Focus on opioids.
- Opioid overuse.
- Other substance abuse.
- Non-functional status.
- Uncertain aetiology of pain.
- Exaggeration of pain.

However, not all of these instruments have been validated and they should not be viewed as diagnostically accurate.[5]

Validated ongoing assessment measures have also been useful in identifying opioid abuse during long-term therapy.[5,6] Current Ministry of Health guidelines recommend the DIRE screening tool.[2]

A positive result with any of these risk assessment tools is not necessarily a reason to deny opioids.[6,12] Rather, a positive result indicates a patient in whom close monitoring might be required to minimise their likelihood of opioid abuse and addiction.

Referral for opioid substitution treatment

OST services are available nationwide. For patients in rural regions, however, the establishment of special dispensing procedures may be necessary if travel time to a pharmacy is prohibitive.

Expert comment: Specialist OST services are available in all the main centres of New Zealand, with many having outreach clinics to cover their catchment area. Referral pathways differ between services, and the specialist service should be contacted in the first instance to determine the referral pathway. The introduction of buprenorphine/naloxone (Suboxone), and the option for second-third daily dosing, may alleviate some of the difficulties with access to pharmacies.

Assessment and diagnosis

An initial, as well as an ongoing, process of comprehensive assessment for recovery is required for all patients.[2] Such an assessment helps to underpin the process of recovery care planning.

A comprehensive assessment of patient suitability for OST should occur within the 2-week period from initial assessment to the first dose of OST.[2] The assessment should only be carried out by an appropriately trained and supervised clinician.

The objectives of the initial assessment are to:[2]

- Establish a diagnosis and complete risk assessment.
- Facilitate patient engagement in the treatment.
- Explore the treatment options and assist the patient to make informed decisions about the treatment.
- Document an initial treatment plan that is agreed to by the patient.
- Establish a patient's strengths, treatment-related issues, and recovery potential.

To be suitable for OST, a patient must meet formal diagnostic criteria for opioid dependence.[2] Criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Statistical Classification of Diseases and Related Health Problems (ICD) diagnostic tools are suitable.

Opioid substitution treatment

OST is indicated for all patients who are opioid dependent and have no specific contraindications.[1] OST involves prescribing opioids as a substitute for illicit and prescribed opioids and ensures that people with opioid dependence have access to services that support them in their recovery.

OST is a long-term intervention.[1,2] The key objectives of OST are to improve the physical and psychological health and wellbeing of people who use opioids via:

- Reduction or cessation of illicit or prescription opioid use.
- Reduction or cessation of injecting and the associated risk of blood-borne virus transmission.
- Reduction of overdose risk.
- Reduction of criminal activity.
- Providing support for patient and family recovery.
- Providing access to recovery support systems and networks.

These objectives are achieved by minimising withdrawal symptoms, reducing craving, and blocking the euphoric effects of other opioids.[2] Ongoing treatment enables patients to achieve stability, reduces drug use and crime, and improves health; it should be regularly reviewed to ensure the patient continues to derive benefit.

International studies confirm that OST is effective in the treatment of opioid dependency.[1,13-15] Compared with therapies that do not use opioid replacement therapy, it dramatically reduces levels of illicit opioid use, increases retention in treatment, and reduces the risk of HIV infection.

OST in New Zealand is provided by specialist addiction services and primary health care teams.[16] Transferring the care of OST patients to a shared care arrangement with primary care offers the following benefits:

- Allows specialist services to focus on those with the highest need.
- Normalises the treatment process.
- Ensures seamless delivery of services across providers.

OST provided by specialist services continues to be delivered in prison for patients who were receiving OST prior to entering prison.[16] Patients cannot be established on methadone while in prison custody.

At the end of 2014, the total number of people receiving OST in New Zealand was 5230 with 71% of OST treatment being delivered by specialist services.[16]

Full details of OST are available in the New Zealand Practice Guidelines for Opioid Substitution Treatment 2014.

Medical treatments

Medical treatments for OST can only be started by a specialist OST service.[17]

OST consists of daily administration of methadone (an opioid agonist) or buprenorphine (an opioid partial agonist) with naloxone (an opioid antagonist).[2,17] Methadone and buprenorphine have gradual onsets of effect and are long-acting. The resulting stable level of opioid effect is experienced by the dependent user as neither intoxication nor withdrawal, but more as normal.

Opioid receptors are present throughout the brain and spinal cord, but are also found in the gastrointestinal system and parts of the autonomic nervous system and on white cells.[2] Consequently, opioid drugs exert diverse actions on multiple organ systems. The most prominent effects are, however, exerted on the CNS and the gastrointestinal tract.

OST medication should be commenced with a short period of stabilisation, followed by either ongoing treatment or a withdrawal regimen.[2] The prescriber should monitor for signs of toxicity, and the patient should be told to watch for warning signs of toxicity on initiation and during titration.

The main concern is the concomitant use of opioids with other prescribed or non-prescribed CNS depressants (including alcohol), which carry a risk of overdose.[2] Drug interactions and those caused by concurrent use of other substances have the potential to affect the safety and effectiveness of OST. Interactions that result in increased blood levels of OST medication carry a risk of drowsiness and overdose and those that lead to reduced OST medication levels carry a risk of reduced treatment efficacy.

Full details of OST prescribing, adverse reaction, and drug interaction considerations are available from the New Zealand Formulary.

Methadone

Methadone is a long-acting synthetic opioid-receptor agonist. Its effects are qualitatively similar to those of morphine and other pure agonist opioids.[2] As it has sedating effects, methadone may be the preferred OST option in some patients, especially those with anxiety.

The risk of overdose is highest in the first two weeks of methadone initiation and also where there is concurrent use of other substances, particularly benzodiazepines. Initiation should be undertaken in a closely supervised setting.[2]

Bothersome adverse effects associated with methadone include constipation, dry mouth (and associated dental cavities), increased perspiration, nausea and vomiting, drowsiness, and reduced sexual function.[2] These adverse effects can usually be managed symptomatically or with dose reduction.

QT interval prolongation is a well-documented, potentially life-threatening, risk of methadone treatment.[2] Patients with history for this risk should be screened before and during OST, particularly when the methadone dose is increased and when other potential QTc-prolonging medications are prescribed, e.g. antipsychotic medications, some antidepressants.

Methadone is metabolised by the cytochrome P450 enzyme CYP3A4, and also partially metabolised at CYP2D6.[2] Consequently, there is potential for interaction with other medicines including commonly prescribed antibiotics and anti-fungal drugs, as well as antiviral agents.

Buprenorphine with naloxone

Buprenorphine is available in a combination preparation with naloxone (Suboxone®) as a sublingual tablet. Sublingual tablets, which should not be swallowed as this reduces the bioavailability of the medicine, require more intensive monitoring during dispensing at the pharmacy.

Buprenorphine is a semi-synthetic opioid-receptor partial agonist, i.e. it has opioid agonist and antagonist properties.[2] Naloxone is an opioid-receptor

antagonist. Naloxone is included in Suboxone to discourage IV misuse of the product. Naloxone precipitates withdrawal if the preparation is injected, but it has little effect when the preparation is taken orally.

Generally, patients experience greater mental clarity and associated cognitive functioning than with methadone.[2] This may be an advantage for people who are employed, studying, or driving, and for those taking other sedative medication concurrently.

The most common adverse events associated with buprenorphine include cold or flu-like symptoms, headaches, sweating, sleeping difficulties, nausea, and mood swings.[2] Most adverse effects occur early in treatment and are usually mild and resolve over time.[2] Some symptoms, including constipation, reduced sexual function, and (rarely) increased sweating, can persist for the duration of buprenorphine treatment.[2]

Like methadone, buprenorphine is metabolised by the cytochrome P450 enzyme CYP3A4.[2] Hence, there is potential for interaction with other medicines including commonly prescribed antibiotics and anti-fungal drugs, as well as antiviral agents. However, because of buprenorphine's maximal opioid effect with increasing doses, interactions that cause the inhibition of metabolism at CYP3A4 are likely to be less clinically significant for buprenorphine than with methadone.[2]

Dose reductions may also be easier than with methadone because the withdrawal symptoms may be milder.[2] During induction, buprenorphine is associated with less risk of overdose when combined with other CNS depressants; nevertheless, caution is still required.[2]

Funding considerations

Methadone and buprenorphine with naloxone (special authority required) are currently the only medications funded by PHARMAC for the treatment of opioid dependence (as of January 2016).

Choice of medical treatment

The choice of OST medication is determined by the specialist OST service.[17]

Both buprenorphine and methadone have been established as being generally well tolerated and effective for the treatment of opioid dependence.[2] The choice of which medication to use should be individualised to specific patients. Key differences between buprenorphine and methadone that may be relevant in the selection of medication are summarised in **Table 1**.

Methadone	Buprenorphine†
Full opioid agonist	Partial opioid agonist
Administered orally	Administered sublingually
No funding restrictions	PHARMAC special authority required
No ceiling effect for respiratory depression Risk of overdose: • in induction stage • in combination with other CNS depressants • by opioid-naive people	Ceiling effect for respiratory depression Generally better tolerated than a full agonist in overdose Caution is required if the client is using other CNS depressants
Dose increases within the first four days risky due to methadone's cumulative effect Can take longer to reach a stable dose (usually 3–6 weeks)	Induction better tolerated and easier, although there is a risk of precipitated withdrawal if it is commenced too soon after the last use of a full opioid agonist. Stable doses reached more quickly (usually 3–5 days)
Higher risk of diversion and misuse	Lower risk in situations where monitoring and supervision of consumption is lacking. Risk of diversion and misuse should still be considered Can be taken alternate days
Appears to prolong the QT interval; cardiac arrhythmia adverse events have been reported	Does not appear to induce significant QT prolongation; therefore, maybe better tolerated by people with cardiac problems
Common side-effects: constipation, sleep apnoea and impact on sex hormones	Common side-effects: nausea, headache, and anxiety
Can be used in pregnancy and breastfeeding	Use of Suboxone in pregnancy and breastfeeding is listed as a precaution
Has sedating effects — can be an advantage for anxious patients	Greater mental clarity — can be an advantage for people employed, studying or driving, and those taking other sedative medication
Withdrawal symptoms generally more severe and withdrawal is generally a protracted process	Less severe withdrawal symptoms Easier to transition in and out of treatment
Onset of effect: 30–60 minutes after dose	Onset of effect: 30–60 minutes after dose
Time to peak effect: 2–4 hours after dose	Time to peak effect: 1–4 hours after dose
Time to steady state after dose change: approximately 4 days	Time to steady state after dose change: approximately 7 days
Duration of clinical effect: 16–30 hours	Duration of clinical effect: 8-12 hours (low dose); 24–72 hours (high dose)
Metabolism strongly affected by liver function	Metabolism less affected by liver function
Major drug interactions: • Sedatives, opioid antagonists • CYP450 inducers/inhibitors • Additive risk with other drugs that alter QT interval	Major drug interactions: • Sedatives • Opioid agonists and antagonists • CYP450 inducers/inhibitors

Table 1. Differences between methadone and buprenorphine that may be relevant in choosing an OST medication.[2,18] † As the formulation buprenorphine plus naloxone (Suboxone).

Disadvantages of opioid substitution treatment

The invasiveness of OST is a primary disadvantage from a patient perspective.[17] The restrictions around takeaway doses have been referred to as 'chemical handcuffing'.

Restrictions on takeaways are necessary to prevent patients using multiple doses together to increase the euphoric effect and/or injecting or selling doses.[17] The restrictions have been cited as a potential barrier to accessing OST since daily onsite dosing can interfere with a patient's ability to obtain and retain paid employment and restricts their movements and activities in general. However, patients enter OST having been informed of the limitations associated with dispensing and not all patients need to attend the pharmacy on a daily basis; clinically-stable patients can have up to four takeaway doses per week. Furthermore, second or third daily dosing is possible with buprenorphine/naloxone hence avoiding the need for takeaways.

The most important risk of methadone and other opioid substitute medicines is overdose.[17] The possibility of overdose, which can be fatal, is greatest during commencement of OST followed by the period during and following withdrawal from the treatment. Once a stable dose is achieved (≤12 weeks depending on whether methadone or buprenorphine is used) the risk of overdose is then substantially reduced.

Contraindications for opioid substitution treatment

Methadone and buprenorphine may not be suitable for the following people:[2]

- Those with decompensated liver disease (such as with jaundice and ascites), as these drugs may precipitate hepatic encephalopathy and cause deterioration in the mental state.
- Those with acute asthma and other causes of respiratory insufficiency.

Precautions (although not contraindications) for both medications include high-risk multiple substance use, severe mental illness, low levels of neuroadaptation to opioids, and significant co-existing medical problems.[2]

Psychosocial interventions

OST should be part of an overall multidisciplinary care programme in which people's psychosocial issues are identified and addressed.[2] These include their physical, emotional, and social needs.

Examples of social interventions include support with practical issues in everyday life, such as managing benefits, accommodation, education, training, parenting, and legal problems.[2]

Psychological interventions might include motivational counselling, cognitive behavioural therapy, and contingency management.[2] These therapies can help to increase motivation to quit or reduce substance use and assist with community reintegration.

Psychosocial interventions may also help to mitigate non-adherence with opioids prescribed for pain. A randomised study conducted in the US assessed the benefits of close monitoring and cognitive behavioural motivational counselling in patients with chronic back pain at high risk for opioid misuse.[19] The results revealed that adherence to prescription opioids was improved to that of low-risk patients by behavioural intervention.

Psychosocial interventions should be tailored to individual needs, have defined goals, and be integrated into the overall service delivery system.[2]

Opioid substitution treatment in primary care

Integration of OST into primary care increases accessibility.[1,2] The primary healthcare setting is regarded as the logical environment for the long-term management of patients receiving OST. It permits patients to live as normal a lifestyle as possible within the constraints of treatment.

According to 2014 figures, 27% of the 5230 people receiving OST were being treated by a GP in a shared care arrangement.[16]

Primary care practitioners will usually need support from the specialist system.[2] With mentoring, training, consultation, and referral, patients with complex comorbidity can be effectively managed in primary care. Indeed, the same principles and skills that GPs employ in the management of chronic illness are relevant to the care of patients with opioid dependence.[20]

The current service delivery model for OST services is centred on specialist services and primary healthcare teams.[2] Entry into OST takes place through specialist services. GPs work under authority from a specialist service lead clinician, or a specialist service medical practitioner approved by the lead clinician.

They must do so in accordance with the terms and conditions specified in the Prescribing controlled drugs in addiction treatment: section 24. Misuse of Drugs Act 1975.[2] All clinical and medical staff working with patients on OST are expected to have completed the National Opioid Substitution Training Programme. All pharmacy staff who are regularly involved in the provision of OST must also receive training. Online training modules based on the Ministry of Health 2014 guidelines are available.

When a patient moves to a shared care arrangement with their primary care team, specialist services should continue to provide support to patients and the authorised GP.[2]

According to a 2008 survey conducted in Auckland, incentives for clinic patients stabilised on OST to transfer from secondary to GP care included confidentiality, a holistic approach to their care, continuity of care, increased patient control, convenience, and avoidance of contact with other opioid-dependent people.[21] Barriers to stable patients' transfer included financial cost and attitudes of secondary care staff and patients.

For some secondary care staff and their patients, distrust in the quality of care provided by trained and authorised GPs was a major barrier.[21] In contrast, GP patients rated primary better than secondary care with none stating a likelihood to return to the secondary service within 6 months.

Alternatives to opioid substitution treatment

OST is the appropriate treatment for most people dependent on opioids.[2] There are, however, a range of other options available. These include managed withdrawal, outpatient programmes, residential treatment programmes and therapeutic communities, and self-help groups.

Naltrexone may be a useful relapse prevention tool for people who have ceased opioid use, as it blocks the effect of opioid drugs.[2] In New Zealand, naltrexone is only funded for its use in alcohol dependence.

EXPERT'S CONCLUDING COMMENTS

OST is an evidenced-based treatment for opioid dependence, which is a complex relapsing condition. Patients are now able to have a choice of medication that can be used in their treatment and recovery. The initial uptake of buprenorphine/naloxone (Suboxone) had been quite slow but has significantly increased over recent months. There is an increasing number of people receiving OST that have a range of co-existing mental and physical health problems. The provision of OST in the primary care setting allows patients to continue OST and their recovery and also improves their access to other healthcare. Methadone remains the preferred treatment for pregnant women who are accessing OST as there is greater information available about its safety and efficacy.

In New Zealand, the use of buprenorphine/naloxone in pregnancy is listed as a precaution and the mono-product (buprenorphine) is not available. For women who subsequently become pregnant whilst on buprenorphine/naloxone, the MOH guidelines recommend discussing the risks versus benefits of switching to methadone (MOH Practice Guidelines for OST; Section 6.7.1). The availability of alternative preparations for buprenorphine/naloxone would be welcomed including the film formulation. There has been increasing emphasis on person-centred and recovery-orientated treatment and the Alcohol and Other Drug (AOD) services sector is working on the development of a consumer and peer workforce with members having personal experience of addiction.

TAKE-HOME MESSAGES:

- Opioid dependency places a significant burden on society and the healthcare system.
- With the increased use of opioids to manage chronic pain conditions, GPs should be aware of the potential for prescription opioid dependence in their non-cancer pain patients.
- OST rather than opioid withdrawal is the preferred pharmacological treatment for opioid dependency.
- Patients on OST are more likely than those not on OST to stay alive, not misuse opioids, and be in contact with the treatment system.
- The primary medications used in OST are methadone and buprenorphine plus naloxone (Suboxone).
- The management of opioid dependence requires medical and psychosocial treatment; access to a multidisciplinary team is necessary.
- With specialist support, OST can be effectively managed in the primary care system.

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