Managing long-term high-dose prescription opioids in patients with non-cancer pain

The potential role of sublingual buprenorphine

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Background
Opioids are frequently used to manage chronic non-cancer pain despite the lack of evidence of benefit and clear evidence of opioid-related harms. Patients undergoing high-dose opioid therapy are at risk of multiple complications, such as opioid toxicity, including fatal overdose and opioid dependence.

Objective
This article provides an overview of the pharmacology of buprenorphine and reviews current evidence for the use of high-dose sublingual buprenorphine–naloxone in the pharmacological management of patients at high risk of complications from chronic opioid use.

Discussion
Buprenorphine–naloxone is well tolerated by patients with chronic pain, and has the potential to improve pain scores and affective symptoms. This is exemplified in a case study based on these authors' experience in an addiction medicine setting. As the rates of pharmaceutical opioid prescribing and related harms continue to increase in Australia, buprenorphine–naloxone is a viable option to manage high-risk chronic pain patients who are unable to reduce or cease their opioid use.

OVER THE PAST 20 YEARS, there has been a significant increase in the prescribing of pharmaceutical opioids in Australia, particularly in the category of long-acting formulations and potent opioids such as oxycodone and fentanyl.[1,2] This trend has been attributed to the growing prevalence of chronic non-cancer pain, increased availability of long-acting opioid formulations, and limitations in access to non-pharmacological treatments for chronic pain.[1,3]

While there is an established role for opioids in the treatment of cancer-related pain, evidence supporting opioids for chronic non-cancer pain is weak. Long-term opioid use for non-cancer pain has been associated with poor functional outcomes, increased healthcare utilisation, opioid-induced hyperalgesia, and the development of an opioid use disorder in up to 18% of patients commenced on opioid treatment.[4–7]

Associated with the increase in opioid prescribing is an escalation of opioid-related hospitalisations and deaths.[8] In 2016, most of the 1045 opioid-related deaths in Australia involved pharmaceutical opioids.[9] Between 2016 and 2017, up to 150 patients a day were admitted to hospital with opioid-related harms, including opioid dependence, poisoning or side effects.[10]

This increase in opioid-related mortality and morbidity has resulted in a greater push for more judicious prescribing of pharmaceutical opioids. For patients undergoing high-dose opioid therapy for chronic pain, this may involve reducing or ceasing their opioids.

This article offers an alternative pharmacological approach to opioid reduction or cessation in an addiction medicine setting using sublingual buprenorphine–naloxone.

High-dose opioid therapy for chronic pain

An Australian cohort study found that patients receiving daily opioid doses greater than 90 mg oral morphine equivalent dose (oMED) experienced less pain relief and were more likely to develop complications such as aberrant behaviour and opioid dependence.[11] Opioid toxicity is dose related, and patients taking more than 100 mg oMED have a nine times greater risk of overdose.[12]

Opioid tolerance and opioid-induced hyperalgesia (OIH) are complications of chronic opioid use, contributing to the failure of opioid therapy in chronic pain management. OIH is multifactorial, resulting from sensitisation of spinal cord

neurons with increased pain sensitivity from chronic opioid exposure.[13]

Kappa opioid receptor and dynorphin

A new development in the understanding of chronic pain is the identification of the kappa opioid receptor (KOR) and its endogenous ligand dynorphin. Spinal dynorphin levels increase with chronic pain and it is hypothesised that dynorphin causes toxicity to neurons and, hence, persistent pain.[13,14] In addition to its effect on pain pathways, the KOR system is also involved in the regulation of emotion and motivation.[14] KOR activation causes dysphoria and aversion, most likely through its effects on mesolimbic pathways involved in motivation and reward.[14] This may explain the negative affect and high rates of mood disorders commonly seen in patients with chronic pain.

Treatment of chronic pain

Both Australian and international guidelines highlight the need for a multidisciplinary approach to chronic pain management. Careful assessment of risk is recommended prior to consideration of opioid therapy and daily doses above 80–100 mg oMED should be avoided.[15–17] The Royal Australian College of General Practitioners' guidelines recommend tapering opioids for patients not achieving benefit or for patients at risk of opioid-related harms.[18]

Pharmacology of buprenorphine

Buprenorphine is a partial mu-opioid receptor agonist. It is a potent analgesic at low doses, with a plateauing of effects at higher doses. This 'ceiling effect' explains its relatively low risk of significant respiratory depression and toxicity even at high doses.[19,20] An additional property of buprenorphine is that it is a KOR antagonist, resulting in a reduced risk of hyperalgesia and dysphoria when compared with full opioid agonists.[21]

As a result of its slow dissociation from, and high affinity for, the mu-opioid receptor, buprenorphine has a prolonged duration of effect. Given sublingually, it has a half-life of up to 37 hours, which allows for daily dosing.[22] This is beneficial in treating opioid-dependent patients, where steady serum levels can prevent withdrawal symptoms and cravings.

Buprenorphine is predominantly biliary excreted, and its pharmacokinetics are not affected by age or renal function.[21,23] It has also been associated with less immunosuppression and hormonal dysfunction.[21,23]

Buprenorphine for the treatment of opioid dependence

While buprenorphine is marketed in low-dose sublingual and transdermal formulations for pain management, it is used worldwide in high-dose formulations for the treatment of opioid dependence.

High-dose sublingual buprenorphine is available in film and tablet forms. The most popular formulation for treatment of opioid dependence is a combination product of buprenorphine and naloxone in a 4:1 ratio. Naloxone is added to the preparation to discourage parenteral misuse. It is poorly absorbed sublingually; however, when injected, it attenuates buprenorphine's effect as a result of receptor antagonism.[24]

High-dose sublingual buprenorphine for chronic pain

The literature on high-dose sublingual buprenorphine–naloxone for patients with chronic pain taking long-term opioids includes six low-quality studies, all showing some effectiveness.

A prospective study by Berland and colleagues studied patients with chronic pain experiencing worsening pain and function despite opioid use.[25] This study included patients on significant doses of opioids (median 400 mg oMED) and with multiple comorbidities. Following rotation to buprenorphine–naloxone, 67% of participants reported better pain control and 60% reported better function. New employment was achieved by 7% of patients. Fifteen per cent weaned off buprenorphine–naloxone.

Another prospective study by Pade and colleagues comprised 143 patients with chronic pain and opioid dependence who commenced buprenorphine–naloxone.[26] There was a small but statistically significant reduction in pain scores post-treatment. Sixty five per cent of patients remained in treatment, and a small proportion of patients successfully weaned off opioids.

Induction of high-dose sublingual buprenorphine

As a high-affinity partial agonist, high-dose buprenorphine may result in opioid withdrawal for patients who are opioid tolerant because of buprenorphine's displacement of opioid agonists from receptors – a phenomenon known as 'precipitated withdrawal'. Hence, induction of buprenorphine–naloxone usually requires a period of abstinence from opioids. This can be challenging as opioid abstinence may result in increased pain for opioid-tolerant patients, resulting in treatment dropout. Patients taking long-acting potent opioids, such as fentanyl patches or methadone, are particularly vulnerable to opioid cessation prior to buprenorphine induction.[27]

There are no widely accepted guidelines for high-dose sublingual buprenorphine induction for patients receiving opioids for chronic pain. In the studies reviewed, a common approach was of 'bridging' with a short-acting opioid agonist (eg morphine, hydromorphone) to reduce the duration of abstinence when weaning patients from long-acting opioid agonists.[28,29]

Based on these authors' experience within an addiction medicine setting, all opioid medications are withheld for one to three days depending on the half-life of the medication. Sublingual buprenorphine–naloxone is commenced when the patient develops signs of opioid withdrawal. Symptomatic medications such as paracetamol, ibuprofen and clonidine are prescribed 'as required' for withdrawal symptoms. If the starting dose of buprenorphine–naloxone 2–4 mg is tolerated, the dose can be increased fairly rapidly over four to five days, to a maximum of 32 mg daily. Doses of 16 mg

daily are generally sufficient to overcome opioid withdrawal symptoms.

Relevance in clinical practice

High-dose sublingual buprenorphine is an option in the treatment of pharmaceutical opioid dependence and has been shown to be effective in this patient group.[30] For patients with chronic pain and opioid dependence, the available evidence suggests that buprenorphine–naloxone is well tolerated and does not worsen chronic pain management. Buprenorphine–naloxone has also been shown to be beneficial for patients with chronic pain on long-term opioids because of its improvement in pain and functional outcomes. It is hence a viable pharmacological alternative to potent opioid agonist therapy as a result of its safety profile and chronic pain treatment outcomes.

Patient selection

For patients with chronic pain taking long-term opioids, there is limited literature identifying which patients are likely to benefit from transfer to buprenorphine–naloxone. Appropriate candidates include those with pharmaceutical opioid dependence and patients at risk of opioid-related complications who are unable to reduce their potent opioid medications.

The *International classification of diseases*, 11th revision (ICD-11)[31] and the *Diagnostic and statistical manual of mental disorders*, 5th edition (DSM-5)[32] provide criteria for opioid dependence (Boxes 1 and 2). In the DSM-5 classification, opioid abuse and opioid dependence are combined as a single diagnosis of 'opioid use disorder'. In addition, tolerance and withdrawal criteria are not considered met if patients are using opioids 'solely under appropriate medical supervision', recognising that physiological adaptation is an expected response to continuous exposure to opioids.

The change in nomenclature and classification in DSM-5, with its focus on a continuum and an increased number of criteria, has raised questions about its application in clinical practice, especially in terms of the diagnostic indications for opioid replacement therapy (ORT). However, there appears to be good agreement between the definition of moderate and severe pharmaceutical opioid use disorder and previous definitions of opioid dependence, suggesting that these patients are appropriate for ORT.[31]

Patients at risk of opioid-related complications who are unable to reduce their potent opioid medications could be trialled on buprenorphine–naloxone under the care of health professionals with the appropriate level of expertise in addiction medicine. These include patients with aberrant drug-related behaviours (Box 3) and patients with risk factors for opioid overdose, such as opioid doses greater than 100 mg oMED daily, concurrent sedative use, a history of overdose, and medical comorbidities including respiratory disease and sleep-disordered breathing.[33]

For patients with comorbid medical and psychiatric disease or significant polypharmacy, these authors recommend commencing buprenorphine–naloxone in residential or inpatient settings.

Open discussion about patient expectations of treatment is necessary prior to commencing buprenorphine–naloxone. Although buprenorphine–naloxone has been shown to improve pain scores, this is not recommended to be the only component of patients' chronic pain management. Patients are encouraged to participate in multidisciplinary pain management programs that focus on

Box 1. ICD-11 definition of opioid dependence[32]

Opioid dependence is a disorder of regulation of opioid use arising from repeated or continuous use of opioids. The characteristic feature is a strong internal drive to use opioids, which is manifested by impaired ability to control use, increasing priority given to use over other activities and persistence of use despite harm or negative consequences. These experiences are often accompanied by a subjective sensation of urge or craving to use opioids. Physiological features of dependence may also be present, including tolerance to the effects of opioids, withdrawal symptoms following cessation or reduction in use of opioids, or repeated use of opioids or pharmacologically similar substances to prevent or alleviate withdrawal symptoms. The features of dependence are usually evident over a period of at least 12 months but the diagnosis may be made if opioid use is continuous (daily or almost daily) for at least one month.

Box 2. *Diagnostic and statistical manual of mental disorders*, 5th edition, definition of opioid use disorder[34]

Within a 12-month period, two or more of the following:

1. Opioid use is greater than originally intended, in terms of duration and/or dosage.
2. Attempts to minimise or control opioid use are unsuccessful, even when the patient desires to do so.
3. Obtaining, using and recovering from opioids takes up a significant amount of the patient's time.
4. The patient experiences a strong urge to use opioids.
5. Everyday obligations relating to work, school or home are unmet as a result of recurrent opioid use.
6. Opioid use is continued despite new or exacerbated social or interpersonal problems resulting from opioid use.
7. Opioid use leads to a reduction or cessation of occupational, social or recreational activities.
8. The patient continually uses opioids at times when it is physically hazardous to do so.
9. Opioid use is continued despite new or exacerbated physical or psychological problems likely resulting from opioid use.
10. The patient exhibits signs of tolerance.
11. The patient experiences withdrawal symptoms.

Box 3. Aberrant drug-related behaviours[35]

- Prescription forgery
- Recurrent prescription losses
- Doctor shopping
- Obtaining prescriptions from non-medical sources
- Unsanctioned dose escalations

active self-management strategies to achieve functional goals.

In summary, patients with chronic pain or substance use disorders experience social stigma, which can be a barrier to them accessing treatment, and it is important to approach their treatment in a supportive and non-judgemental way. High-dose sublingual buprenorphine may form part of this therapeutic intervention.

Key points

- Chronic opioid use is increasing in Australia and patients are at risk of complications such as fatal overdose and opioid dependence.
- Buprenorphine–naloxone is well tolerated by patients with chronic pain, and has the potential to improve pain scores and affective symptoms.
- Induction of buprenorphine–naloxone in patients tolerant to opioid agonist treatment carries the risk of precipitated withdrawal.

CASE

A female aged 46 years was referred to the addiction medicine service by her general practitioner (GP) and private pain specialist for worsening pain control despite high-dose opioid medications. She had a long history of low back pain that, despite multiple interventions, was affecting her functional capacity. She reported high pain levels that limited her ability to perform activities of daily living. She was mainly housebound because of a low tolerance for walking and standing.

Her past medical history of significance included obesity, obstructive sleep apnoea and an episode of respiratory arrest following severe pneumonia. She had been diagnosed with depression and described long-standing anhedonia that worsened following her rotation from methadone to fentanyl a few years ago. Her treatment included transdermal fentanyl 150 ug/hr applied every three days (ie approximately 450 mg oral morphine equivalent dose [oMED] daily). She experienced side effects of constipation and drowsiness. She had been unable to reduce this medication despite recommendations to do so. There was no non-medical use or other aberrant opioid-related behaviours.

Her treatment plan with the service involved replacement of fentanyl with buprenorphine–naloxone sublingual film to manage opioid toxicity risk. She was admitted to the residential detoxification unit and her fentanyl patch removed. On day two of the admission, she developed opioid withdrawal symptoms, and buprenorphine–naloxone was commenced. She tolerated the transition well, and her dose was titrated to 32 mg daily. On questioning, she reported less sedation and improved cognitive clarity on buprenorphine–naloxone. She remained stable on this medication regimen nine months after treatment initiation.

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