A RESEARCH REVIEW™ EDUCATIONAL SERIES

Opioid substitution therapy: Co-morbid chronic pain and opioid dependence

Making Education Easy 2017

About the Reviewer

Dr Richard McGrath

After graduating in 1985, Richard McGrath spent seven years doing hospital and locum GP jobs in the Wellington area, then joined a general practice in Masterton in 1993, retiring from full time work there in 2011. He has worked for the local addiction service since 1995. For the past four years he has spread his time between Masterton-based work as a locum GP, addictions and police medical officer, and contract work as senior medical officer at Australia's Christmas Island immigration detention centre.

The opioid-dependent patient with concurrent chronic pain presents a unique challenge for healthcare providers, especially in the primary care setting. This article provides an overview of the treatment of opioid dependence in patients who have co-morbid chronic pain, with consideration of the phenomenon of hyperalgesia. This review is sponsored by an educational grant from Indivior Pty Ltd.

The number of patients with chronic pain being treated with opioids has increased markedly over the past two decades, with an accompanying increase in opioid dependency.[1,2] Consistent with this trend, a retrospective analysis of a large healthcare database in the US found a 35% prevalence of opioid-use disorder among outpatients receiving long-term opioid therapy for chronic non-cancer pain (CNCP).[3] Additionally, a systematic literature review found a nearly 60% prevalence of pain symptoms in substance use treatment populations reporting non-prescription opioid use.[4]

Individuals with co-occurring opioid dependency and chronic pain require treatment that targets both these comorbidities.

Treatment

The NZ Practice Guidelines for opioid substitution therapy (OST) recommend that OST services and GP prescribers should consult with specialist pain services about the management of patients with comorbid CNCP and opioid dependency.[5] Initial treatment of such patients may involve temporary opioid analgesic abstinence followed by cognitive behavioural therapy and the use of non-opioid analgesics.[6] An alternative option is OST using either methadone or buprenorphine, both of which appear to be to be equally effective in this setting.[7,8]

Methadone has been demonstrated to be effective as an analgesic and for OST.[9-11] A recent systematic literature review suggests that treating OST patients with methadone as a pain management strategy may be preferable to using other opioid analgesics.[10] However, methadone has adverse effects common to all full mu (μ)-opioid receptor agonists (e.g. constipation, respiratory depression at high doses) and serious adverse events related to its long half-life (e.g. drug overdose, death) that limit its effectiveness.[9,11]

As a partial μ-opioid agonist, buprenorphine has a lower risk of overdose and is used as an alternative to methadone for OST, but still has analgesic properties.[12,13] Despite having a ceiling effect for respiratory depression at high doses, no relevant analgesic ceiling effect is observed with buprenorphine.[14,15] Also, buprenorphine has less abuse liability than methadone.[16,17] Hence, it comes with less regulation and without the social stigma of methadone.[18,19]

Buprenorphine is an opioid with a complex pharmacology.[20] Due to its partial stimulation of the μ-opioid receptor, buprenorphine is a weak analgesic.[21,22] However, it has multiple mechanisms of action that contribute to an overall analgesic activity without a ceiling effect and with no antagonism of the analgesic effects of other μ-opioid receptor agonists.[23-25] By virtue of multiple signal transduction pathways, a drug can be a full agonist on one therapeutic effect and a partial agonist on another.[26]

Regardless of the mechanism, the clinical analgesic efficacy of buprenorphine has been established.[26] Retrospective and non-comparative clinical studies provided initial evidence that buprenorphine reduces pain in patients with CNCP who were also opioid dependent.[27-29] In a randomised controlled trial in patients with CNCP and co-existent opioid dependence, continuous low-dose buprenorphine and methadone both produced a statistically significant reduction in pain after 6 months (**Figure 1**).[30] Although the total analgesic effect produced by both agents was small the severity of the chronic pain in the patient sample was high. An absence of dose escalations and worsening of pain further supported the analgesic efficacy of the two treatments.

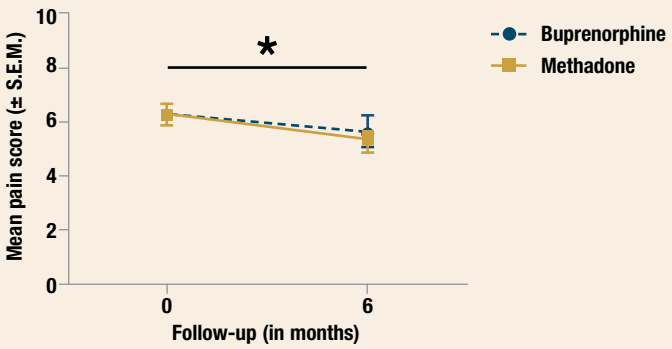

Figure 1. Baseline reductions in pain score in opioid-dependent patients with CNCP treated with long-term buprenorphine or methadone.[30] Significant difference vs baseline: *p=0.043.

In addition, an observational study that demonstrated a statistically significant reduction in pain in patients with chronic pain and opioid dependence during buprenorphine OST also provides support for the use of buprenorphine in this setting.[31]

Hyperalgesia

Many patients with chronic pain develop pharmacological tolerance to traditional opioids with long-term use and some patients even develop a paradoxical increase in pain perception rather than an anti-nociceptive effect.[32-34] These physiological phenomena can undermine the clinical usefulness of opioids.

The phenomenon of nociceptive sensitisation developing with chronic opioid use is known as opioid-induced hyperalgesia (OIH). Currently, there is no ideal agent for the treatment of OIH.[35] Treatment should involve tapering or discontinuation of the current opioid, consideration of opioid switching, adding a NMDA receptor agonist such as ketamine, and/or adding a non-opioid analgesic such as an NSAID. Methadone may have a limited role given evidence of increased sensitivity to some types of pain in patients with chronic pain managed on methadone and in people receiving methadone OST.

There is preclinical and clinical study evidence as well as expert opinion that buprenorphine has anti-hyperalgesia effects.[15,36,37] For example, buprenorphine produced durable anti-hyperalgesia effects in a randomized, double-blind, placebo-controlled study using an experimental pain model in healthy human volunteers.[38] Additionally, in an open-label follow-up study, buprenorphine provided at least satisfactory pain relief in 90% of patients in the long-term management (mean duration 7.5 months) of chronic cancer or non-cancer pain.[39]

The mechanism by which buprenorphine moderates hyperalgesia is unclear but may involve its activity at the κ (kappa)-opioid receptor.[20] As a full κ-opioid antagonist, in addition to being a partial μ-opioid agonist, buprenorphine can compete with the κ-opioid receptor antagonist spinal dynorphin, which appears to contribute to OIH.[22] This competition at the κ-opioid receptor may attenuate the effect of spinal dynorphin thereby attenuating OIH.

EXPERT'S CONCLUDING COMMENTS

The use of a sublingual buprenorphine/naloxone combination in treating those with opioid dependence is now well established across addiction services. This formulation is not currently indicated for therapeutic use by pain clinics as an option for symptom control, though a transdermal buprenorphine patch is available. For patients with chronic pain syndromes, non-pharmacological measures such as lifestyle adjustment and physical and cognitive therapy are important and effective tools in relieving discomfort. Unfortunately, problems such as tolerance and adverse effects often limit the usefulness of analgesic medication.

Although effective in the management of severe acute pain, the ongoing use of opioid agonists such as methadone, oxycodone, and fentanyl in those with chronic pain can result in a paradoxical worsening of symptoms. Buprenorphine, with its unique action on opioid receptors and superior safety profile, appears an attractive option for clinicians wanting to avoid hyperalgesia. The development of chronic pain syndromes in people already on treatment for opioid dependence offers a particular challenge. There is a growing cohort of older patients on opioid substitution treatment at risk of developing degenerative, malignant, and other conditions that may result in long-term pain. For those already on buprenorphine/naloxone maintenance treatment, some studies indicate that it may be possible to increase the doses used beyond the upper limit of the recommended range for treating dependence, while avoiding some of the side effects commonly found when using pure opioid agonists.

TAKE-HOME MESSAGES

- Chronic pain appears to be common in people with opioid dependence, including those receiving OST.
- Patients with concurrent pain and opioid dependence are best managed by a multidisciplinary team that includes both pain and OST specialists.
- Methadone is an effective OST and has analgesic effects but its utility is limited by its safety profile and elevated risk of overdose.
- Buprenorphine is also an effective OST and has a ceiling effect on respiratory depression but not analgesia.
- Hyperalgesia is a less recognized side effect of long-term opioid therapy but may be increasingly encountered as more patients receive opioids for chronic pain.
- Buprenorphine appears to have a low level of pharmacological tolerance and hyperalgesia, and can be used with other μ-opioid receptor agonists.

REFERENCES

1. Salsitz EA. Chronic pain, chronic opioid addiction: a complex nexus. J Med Toxicol. 2016;12(1):54-7.
2. Juurlink DN, et al. Dependence and addiction during chronic opioid therapy. J Med Toxicol. 2012;8(4):393-9.
3. Boscarino JA, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. J Addict Dis. 2011;30(3):185-94.
4. Lusted A, et al. Prevalence of pain among nonmedical prescription opioid users in substance use treatment populations: systematic review and meta-analyses. Pain Physician. 2013;16(6):E671-84.
5. Ministry of Health. New Zealand practice guidelines for opioid substitution treatment 2014. Wellington: Ministry of Health. 2014. Available from: http://www.health.govt.nz/publication/new-zealand-practice-guidelines-opioid-substitution-treatment-2014.
6. Blondell RD, et al. Treating opioid dependency and coexistent chronic nonmalignant pain. Am Fam Physician. 2008;78(10):1132-3.
7. Gowing L, et al. Buprenorphine for managing opioid withdrawal. Cochrane Database Syst Rev. 2017;2:Cd002025.
8. Nielsen S, et al. Opioid agonist treatment for pharmaceutical opioid dependent people. Cochrane Database Syst Rev. 2016(5):Cd011117.
9. Rhodin A, et al. Methadone treatment of chronic non-malignant pain and opioid dependence--a long-term follow-up. Eur J Pain. 2006;10(3):271-8.
10. Taveros MC, et al. Pain management strategies for patients on methadone maintenance therapy: a systematic review of the literature. BMJ Support Palliat Care. 2016.
11. Methadone Data sheet (Biodone, Biodone Forte, Biodone Extra Forte). 24 June 2014. Auckland: Biomed Limited. http://medsafe.govt.nz/profs/Datasheet/b/Biodoneoralsoln.pdf.
12. Heel RC, et al. Buprenorphine: a review of its pharmacological properties and therapeutic efficacy. Drugs. 1979;17(2):81-110.
13. Johnson RE, et al. Buprenorphine: considerations for pain management. J Pain Symptom Manage. 2005;29(3):297-326.
14. Ling W, et al. Prescription opioid abuse, pain and addiction: clinical issues and implications. Drug Alcohol Rev. 2011;30(3):300-5.
15. Pergolizzi J, et al. Current knowledge of buprenorphine and its unique pharmacological profile. Pain Pract. 2010;10(5):428-50.
16. Ducharme S, et al. Update on the clinical use of buprenorphine: in opioid-related disorders. Can Fam Physician. 2012;58(1):37-41.
17. Mauger S, et al. Utilizing buprenorphine-naloxone to treat illicit and prescription-opioid dependence. Neuropsychiatr Dis Treat. 2014;10:587-98.
18. Bonhomme J, et al. Opioid addiction and abuse in primary care practice: a comparison of methadone and buprenorphine as treatment options. J Natl Med Assoc. 2012;104(7-8):342-50.
19. Stock C, et al. Bupreorphine:a new pharmacotherapy for opioid addictions treatment. J Pain Palliat Care Pharmacother. 2004;18(3):35-54.
20. Lutfy K, et al. Buprenorphine: a unique drug with complex pharmacology. Curr Neuropharmacol. 2004;2(4):395-402.
21. Suboxone Data Sheet (buprenorphine + naloxone). 28 September 2016. Auckland: Pharmacy Retailing (NZ) Ltd. Available from: http://www.medsafe.govt.nz/profs/Datasheet/s/Suboxonetab.pdf.
22. Chen KY, et al. Buprenorphine-naloxone therapy in pain management. Anesthesiology. 2014;120(5):1262-74.
23. van Niel JC, et al. Efficacy of full micro-opioid receptor agonists is not impaired by concomitant buprenorphine or mixed opioid agonists/antagonists - Preclinical and clinical evidence. Drug Res (Stuttg). 2016;66(11):562-70.
24. Butler S. Buprenorphine – Clinically useful but often misunderstood. Scandinavian Journal of Pain. 2013;4(3):148-52.
25. Breivik H. Buprenorphine – The ideal drug for most clinical indications for an opioid? Scandinavian Journal of Pain. 2013; 4(3):146-7.
26. Raffa RB, et al. The clinical analgesic efficacy of buprenorphine. J Clin Pharm Ther. 2014;39(6):577-83.
27. Daitch J, et al. Conversion of chronic pain patients from full-opioid agonists to sublingual buprenorphine. Pain Physician. 2012;15(3 Suppl):Es59-66.
28. Pade PA, et al. Prescription opioid abuse, chronic pain, and primary care: a Co-occurring Disorders Clinic in the chronic disease model. J Subst Abuse Treat. 2012;43(4):446-50.
29. Roux P, et al. Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain: reduction of pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone. Pain. 2013;154(8):1442-8.
30. Neumann AM, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. J Addict Dis. 2013;32(1):68-78.
31. Worley MJ, et al. Pain volatility and prescription opioid addiction treatment outcomes in patients with chronic pain. Exp Clin Psychopharmacol. 2015;23(6):428-35.
32. Chu LF, et al. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. Clin J Pain. 2008;24(6):479-96.
33. Lee M, et al. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14(2):145-61.
34. Roeckel LA, et al. Opioid-induced hyperalgesia: Cellular and molecular mechanisms. Neuroscience. 2016;338:160-82.
35. Ramasubbu C, et al. Pharmacological treatment of opioid-induced hyperalgesia: a review of the evidence. J Pain Palliat Care Pharmacother. 2011;25(3):219-30.
36. Hans G. Buprenorphine--a review of its role in neuropathic pain. J Opioid Manag. 2007;3(4):195-206.
37. Khanna IK, et al. Buprenorphine - an attractive opioid with underutilized potential in treatment of chronic pain. J Pain Res. 2015;8:859-70.
38. Koppert W, et al. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. Pain. 2005;118(1-2):15-22.
39. Likar R, et al. Long-term management of chronic pain with transdermal buprenorphine: a multicenter, open-label, follow-up study in patients from three short-term clinical trials. Clin Ther. 2006;28(6):943-52.