epal
An informative read of news, studies, facts & help

Grampians Regional Palliative Care Team

# OPIOID REPLACEMENT THERAPY IN PALLIATIVE MEDICINE

**Background**

Specialist palliative care providers are likely to be familiar with the use of oral methadone and transdermal buprenorphine for treating complex cancer pain syndromes and in the case of buprenorphine, chronic cancer and sometimes non-cancer pain.

Both of these medications however are used in the treatment of opioid dependency, which has implications for the palliative care context.

Approximately 14000 Victorians take opioid replacement therapy (ORT) on a daily basis, supervised by a specially trained prescriber and their community pharmacist.[1] ORT is associated with decreased all cause and drug harm mortality.[2] ORT is considered so effective at reducing opioid related harm in the community that methadone is listed on the WHO list of essential medicines for treating opioid addiction.[3]

Opioid replacement programs cater for a vulnerable section of the community, many of whom have comorbid health conditions such as hepatitis C and smoking related illnesses.[4] ORT clients are also less likely to participate in population screening programs such as cervical screening.[4] The majority of ORT clients in Australia are aged between 30 and 49 years, however a growing minority (8.1% in 2019) of clients are aged over 60 years.[1] It is therefore increasingly likely that palliative care providers will see patients who are being treated with ORT, in addition to managing their terminal illness and this has implications for care.

**Opioid replacement therapy options.**

ORT clients are prescribed oral methadone liquid, sublingual buprenorphine (in a film preparation combined with naloxone or in a tablet) or a long acting (weekly or monthly) injectable buprenorphine formulation.

**Methadone in palliative care patients.**

When used for ORT, methadone is prescribed in a liquid formulation *(Biodone Forte*) which is diluted by the pharmacist to a volume of at least 200mL. Patients are required to collect and take their dose from their pharmacy on a daily basis, unless they are eligible for takeaway doses. Patients at the end of life may struggle with the diluted volume or attending for dosing and collaboration with the ORT prescriber is critical to determine feasible options for the individual patient.

ORT clients prescribed methadone in the setting of a life-limiting illness can continue on their background methadone under the care of their usual ORT prescriber if appropriate. If pain becomes a problem, there are several important management considerations, as methadone taken for ORT may not provide the analgesic benefit required to manage acute pain situations. Patients on high doses of methadone may be relatively resistant to standard opioid doses commonly prescribed for symptom management in terminal illnesses. Careful use of non-opioid adjuvant analgesics and non-pharmacological and interventional approaches may be helpful additions to opioids.

For patients who require opioid analgesia, there are several potential approaches that can be considered in conjunction with the patients regular ORT prescriber and GP.

Firstly, some patients continue on their usual methadone dose for ORT and an additional opioid analgesic is added to the regimen to address concurrent symptoms such as cancer pain. In this situation, the ORT is maintained and the additional opioid titrated to achieve the desired effect.

Secondly, for some ORT patients, additional analgesic benefit can be obtained by dividing their normal methadone dose into two or three divided doses over the course of the day. This approach has practical limitations for patients who are not suitable for take-away doses. In limited situations, it may be feasible to transition patients who have successfully been on long term ORT, with a stable and supportive psychosocial environment to oral methadone tablets as part of the management of complex cancer pain, however this will not be feasible for all patients.

Non-opioid options such optimising the use of paracetamol, steroids and non-steroidal anti-inflammatories, antidepressants, anticonvulsants and other adjuvant analgesics should be considered. Consideration should also be given to palliative radiotherapy for pain relief and the use of nerve blocks and other interventional techniques when feasible. As with any palliative care patient, it is also important to consider the patient's total pain experience, and optimise the management of co-morbid conditions such as depression and anxiety. The impact of carer stress and other social factors should also be considered.

When selecting a PRN opioid dose for a patient taking methadone for cancer pain, it can be helpful to refer to the previous alternative opioid dose as a guide. This is generally not possible for patients on ORT and the current dose of methadone cannot be used to calculate a PRN dose of an alternative opioid. In the absence of an established conversion method, it may be sensible to start at the upper end of the typical starting range for the medication being used and quickly titrate to effect.

For patients in the terminal phase (or who have another reason to be unable to take their normal liquid dosing), subcutaneous methadone can be used. The conversion between oral and subcutaneous dosing is in the order of 50-80% and so for safety, half of the usual daily oral dose can be given subcutaneously over twenty-four hours in a syringe driver.[5-6] Methadone can be irritating when given subcutaneously and so the addition of a small (e.g. 1mg) dose of dexamethasone via the subcutaneous line or in the infusion can be considered. Again the appropriateness of subcutaneous methadone in the community setting will vary according to the individual patient.

**Buprenorphine in palliative care patients.**

Buprenorphine is available in a sublingual film in a fixed dose combination with naloxone *(Suboxone)*, a tablet *(Subutex*) and a long acting subcutaneous injection lasting one week (*Buvidal Weekly)* or one month *(Buvidal Monthly or Sublocade)* depending on the preparation. Buprenorphine is often used in higher doses when used for ORT compared with pain management in palliative care or chronic pain settings. Typically, doses of 12-24mg (approximately 900-1800mg oral morphine equivalent (OME)) are required, although up to 32mg/day may be necessary.[7] For reference, a 40mcg/hr strength buprenorphine patch provides about 0.96mg/day (approximately 100mg OME).[8]

Buprenorphine is a partial mu agonist with a ceiling effect for respiratory depression and euphoria, but without a clear analgesic ceiling effect in humans.[9] As a result, buprenorphine is considered a safer drug to use in ORT compared with methadone.

As buprenorphine binds to the μ receptor with greater affinity than other opioids, it has the potential to antagonise other opioids used for analgesia. Practically, this is thought to be most problematic with doses of buprenorphine above 16mg/day.[10] Studies of transdermal and oral buprenorphine up to 1.6mg/day have suggested that morphine can still be used effectively for breakthrough pain, however patients on higher doses of buprenorphine may respond less to full μ agonists like morphine and require higher doses for effective analgesia. [11-13] Due to the potential difficulties associated with analgesia and buprenorphine ORT in patients with life limiting illnesses, rotating to methadone is often considered.

The combination buprenorphine/naloxone preparation is designed to reduce the risk of misuse, as the naloxone component will precipitate unpleasant withdrawal effects or decrease the effect of the buprenorphine component if injected. The combination product is contraindicated however in patients with moderate to severe hepatic failure as the naloxone component may be incompletely metabolised by first pass metabolism in these patients.[14] This is similar to the problems encountered by palliative care patients with hepatic failure who are prescribed combination oxycodone/naloxone. For this reason, patients with hepatic failure who are normally maintained on the combination product may do better on single agent buprenorphine or methadone for ORT.

Subcutaneous depot buprenorphine is a relatively new option and is promoted as a more convenient option for patients who do not wish to attend for daily pick-ups and a modality less prone to diversion or misuse, as the depot is administered by a registered health practitioner. Instinctively, it would seem that this option may be suitable for palliative care patients who may struggle with the logistics of oral buprenorphine, notwithstanding the issues surrounding analgesic efficacy when treating concurrent pain. There is currently no established role for the use of subcutaneous buprenorphine as a replacement for oral dosing in ORT patients at the end of life specifically. There may be a role however for further research to establish the utility of this option in cases where it is felt to be clinically appropriate to continue buprenorphine for ORT in the dying.

**Legal requirements to prescribe.**

Palliative care practitioners should be mindful of the legal requirements to prescribe Schedule 8 medications in Victoria. Patients taking ORT are automatically considered drug-dependent persons and so prescribers must obtain a permit prior to prescribing a Schedule 8 medicine.[15] The only exemptions to this requirement are for patients who are being treated in a hospital or emergency department, prison or residential aged care facility. Practically, this means that patients taking ORT may need to be admitted to hospital to manage unexpected deterioration unless there has been a clearly developed plan made in advance to manage deterioration in the community.

**Safety and diversion considerations.**

The choice and appropriateness of PRN (and non-ORT long acting) opioids in the community will vary according to the clinical situation. All medications can cause harm and have the potential for abuse, regardless of their formulation. For example, one 64mg tablet of controlled release hydromorphone (the equivalent of 320mg of oral morphine) may be far more harmful than an ampule of 10mg per mL strength morphine (the equivalent of 30mg of oral morphine). Strategies such as limiting prescribed quantities, increasing the frequency of pick-ups from the treating pharmacy and careful planning of storage options may be helpful. In addition, an opioid contract with clear plans for regular and reliable access, replacement of lost or stolen medication and clear mechanisms for reassessment should the clinical situation change may be helpful in setting expectations and reducing the risk of inadequate treatment.[16]

**Conclusion**

In summary, ORT patients are increasingly likely to require palliative medicine services to assist with their management at the end of life as the cohort ages. Once an ORT patient has been diagnosed with a life-limiting illness, consideration should be given to how good symptom management and end of life care can be achieved, whilst allowing the patient to continue to benefit from the stability of ORT. This may require the modification of existing ORT arrangements. Collaboration between providers is essential for the delivery of safe and individualised care.

**References**

1. Australian Institute of Health and Welfare. National Opioid Pharmacotherapy Statistics Annual Data collection 2019 [Internet]. Canberra: Australian Institute of Health and Welfare, 2020 [cited 2020 Jul. 22]. Available from: https://www.aihw.gov.au/reports/alcohol-other-drug-treatment-services/national-opioid-pharmacotherapy-statistics-2019

2. Pearce LA, Min JE, Piske M, et al. Opioid agonist treatment and risk of mortality during opioid overdose public health emergency: population based retrospective cohort study. BMJ. 2020;368:m772. Published 2020 Mar 31. doi:10.1136/bmj.m772
3. World Health Organisation. World Health Organisation model list of essential medicines [Internet]. Geneva: World Health Organisation; 2019 [cited 2020 Jul 23]. 62 p. Available from: https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1
4. Islam MM, Taylor A, Smyth C, Day CA. General health of opioid substitution therapy clients. Intern Med J. 2013;43(12):1335-1338. doi:10.1111/imj.12298
5. Mathew P, Storey P. Subcutaneous methadone in terminally ill patients: manageable local toxicity. J Pain Symptom Manage. 1999;18(1):49-52. doi:10.1016/s0885-3924(99)00020
6. Centeno C, Vara F. Intermittent subcutaneous methadone administration in the management of cancer pain. J Pain Palliat Care Pharmacother. 2005;19(2):7-12.
7. Australian Medicines Handbook 2020 (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2020 July. Available from: https://amhonline.amh.net.au/
8. Twycross R, Wilcock A, Howard P, editors. PCF 6 Palliative care formulary. London: Pharmaceutical press; 2018. 399 p.
9. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96(5):627-632. doi:10.1093/bja/ael051
10. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;(2):CD002207. Published 2014 Feb 6. doi:10.1002/14651858.CD002207.pub4
11. Mercadante S, Villari P, Ferrera P, et al. Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine. J Pain Symptom Manage. 2006;32(2):175-179. doi:10.1016/j.jpainsymman.2006.01.013
12. Kornfeld H, Manfredi L. Effectiveness of full agonist opioids in patients stabilized on buprenorphine undergoing major surgery: a case series. Am J Ther. 2010;17(5):523-528. doi:10.1097/MJT.0b013e3181be0804
13. Heit HA, Gourlay DL. Buprenorphine: new tricks with an old molecule for pain management [published correction appears in Clin J Pain. 2008 May;24(4):370]. Clin J Pain. 2008;24(2):93-97. doi:10.1097/AJP.0b013e31815ca2b4
14. Strain E. Pharmacotherapy for opioid use disorder. In: Basow DS, ed. Up-to-Date [database on the Internet]. Waltham (MA): UpToDate; 2020 [cited 2020 Aug 24]. Available from: http://www.uptodate.com
15. health.vic [Internet]. Melbourne VIC: State Government Victoria; c2017-2020 . Schedule 8 permits and notifications; 2020 [cited 2020 Aug 24]; [about 2 screens]. Available from: https://www2.health.vic.gov.au/public-health/drugs-and-poisons/patient-schedule-8-treatment-permits/schedule-8-permits-and-notifications
16. The Royal Australian College of General Practitioners. Prescribing drugs of dependence in general practice, Part C1: Opioids. East Melbourne, Vic: RACGP, 2017.

**Dr Eve Westland**
Palliative Medicine Specialist
Grampians Regional Palliative Care Team