Cancer pain management

What are the controversies?

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Adequate pain relief in people with advanced cancer can usually be achieved using an evidence-based, multidisciplinary approach. However, some patients experience refractory cancer pain, with clinicians then understandably turning to controversial therapeutic options. This article considers some of these therapeutic options and the evidence supporting or cautioning against their use.

Pain is a major source of distress in patients with advanced cancer. Almost half of all patients with metastatic cancer report moderate-to-severe pain with increasing prevalence prior to death.[1] Adequate pain relief can usually be achieved using an evidence-based, multidisciplinary approach.[2] Nevertheless, 10 to 20% of patients will experience refractory cancer pain.[2]

Clinicians will understandably turn to controversial therapeutic options once standard care fails. Controversial therapies are defined in this article as those that have produced considerable disagreement in the palliative care literature, particularly regarding the degree to which they are supported by evidence. The evidence base behind most of these second-line practices is often reliant on anecdote and/or personal experience and often supported by reports of significant benefit. This article considers some of these contentious pharmacological options and the evidence supporting or cautioning against their use and includes the authors' opinion as to their value.

Key points

- **The benefit of the World Health Organization analgesic ladder in facilitating pain relief in patients with cancer outweighs the criticisms.**
- **The prescription of opioid analgesia should be individualised to the needs and preferences of patients.**
- **Methadone can be a useful drug in refractory cancer pain but is best left to specialists in view of the potential for harm.**
- **The use of ketamine for chronic cancer pain is not supported by the existing evidence.**
- **Given the lack of high-quality evidence of clinical benefit, it is hard to recommend medicinal cannabis as standard practice for cancer pain management.**

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World Health Organization analgesic ladder

There is little controversy about the historical benefit of the World Health Organization (WHO) ladder per se and its significant role in bringing pain relief to many people worldwide. However, there has been much discussion about its relevance in recent times and concerns have been raised about its deleterious effect in the management of nonmalignant pain. The comments in this article relate to its use in cancer pain.

The WHO analgesic ladder was first published in 1986 as an approach to cancer pain management relevant to both developed and developing health services.[3] It is simple, easy to understand and utilises a small number of commonly used analgesics. A three-step approach to cancer management is advocated, corresponding to three levels of pain severity (mild, moderate, severe).

- Step 1: start a nonopioid (e.g. paracetamol) with or without an adjuvant analgesic, then
- Step 2: add a weak opioid (e.g. codeine, tramadol) with or without an adjuvant analgesic, then
- Step 3: replace the weak opioid with a strong opioid (e.g. morphine, oxycodone).

To place these recommendations in the appropriate historical context, the first hospice was opened in 1967, the term 'palliative care' was first coined in 1974, and the first slow-release opioid was introduced in 1980.[4-6]

Options for cancer pain are now more plentiful and pain management more complex, leading many authors to suggest that the WHO ladder needs modification to avoid obsolescence.[7] For example, it does not take into account the mechanism, type or cause of pain, it does not consider interventional pain procedures and it suggests a one-way escalation of opioids.[8]

One major European guideline suggests that low-dose strong opioids should be used as first-line agents for moderate cancer pain rather than the WHO ladder's recommendation of weak opioids at step 2.[1] This is echoed in a regularly updated Australian guideline.[9] As others have noted, this approach seemingly transforms the WHO ladder into the WHO elevator, where the patient proceeds directly to the appropriate level rather than climbing one rung at a time.[7]

A multicentre, open-label randomised controlled trial (RCT) in adults with moderate cancer pain showed low-dose morphine resulted in a 20% pain intensity reduction for 88.2% of patients versus 57.7% in the weak opioid group.[10] Another RCT supported the omission of step 2, although there were some questions around study methodology.[11,12]

The reliance on opioids in the WHO ladder raises issues around opioid dependency as survival is more prolonged.[13] Moreover, it has received a portion of the blame for current opioid epidemics following its use in patients with chronic nonmalignant pain.[14] Radiotherapy, chemotherapy, surgery or interventional pain procedures may all decrease the daily opioid requirement. Patients who have improved pain control after these treatments should be considered for gradual opioid dose reduction.

Authors' opinion: the benefit of this simple tool in facilitating pain relief in patients with cancer outweighs the criticisms. There is evidence to support the common practice of omitting the second level of the WHO ladder (use of a weak opioid) in the management of cancer pain.

Regular long-acting or as-required opioids

Regular dosing 'by the clock' is one of the recommendations of most international analgesic guidelines. Usual practice is to titrate short-acting opioids upwards until pain control is achieved, at which time the total opioid dose used can be converted to a long-acting preparation to be taken regularly every day. Pain varies, however, and many patients prefer to take analgesia only when required. Moreover, several guidelines now recommend titration with either long- or short-acting opioids.[1]

A systematic review of RCTs that compared regular with as-required analgesia did not demonstrate superiority of regular analgesia.[15] Moreover, regular dosing was associated with significantly higher total opioid doses. This is relevant for patients wishing to maintain full cognitive function.

Authors' opinion: the prescription of opioid analgesia should be individualised to the needs and preferences of patients.

Methadone

Methadone is a synthetic opioid developed in the 1930s. Its main use today is in methadone maintenance programs, as the long half-life of the drug allows for once-daily delivery. In palliative care, methadone is generally reserved for patients with pain that is difficult to manage with standard analgesia. It is thought by many that methadone is more efficacious than other opioids, especially in the management of neuropathic pain. Based on low-quality evidence, a 2017 updated Cochrane review concluded that methadone has similar analgesic benefits to morphine.[16] In this 2017 Cochrane review, the drawbacks of methadone were pointed out and included 'high potential for accumulation leading to delayed toxicity, highly variable pharmacokinetics between individuals, relative ease of use of modified-release morphine preparations, possible drug interactions, and concerns over dose titration and conversion from other opioids'.[17] Similarly, the evidence of benefit in patients with neuropathic pain is limited and of low quality.[17]

Many clinicians prefer to use methadone as an adjuvant because conversion from other opioids is notoriously difficult. Multiple conversion methods have been published, resulting in widely differing doses of methadone when compared head-to-head.[18]

Authors' opinion: methadone can be a useful drug in refractory cancer pain but is best left to specialists in view of the potential for harm.

Opioid rotation

Opioid rotation is the act of switching from one opioid to another to improve pain control or decrease adverse effects. There are multiple

anecdotal reports of benefit after such switching. The purported mechanism underlying the benefit of opioid rotation remains unclear. The original hypothesis of toxic metabolite reduction remains unconfirmed. Incomplete cross-tolerance has been suggested as an alternative mechanism. This theory suggests that although patients become generally tolerant to opioids with regular dosing, the tolerance incompletely carries over when another opioid is prescribed.[19] Differential agonism of opioid receptor subtypes has also been proposed.[19]

Opioid rotation was first evaluated in a retrospective cohort study of 191 consecutive palliative patients.[20] From this cohort, 80 patients underwent opioid rotation. The indications were persistent pain as well as other symptoms of opioid toxicity such as cognitive decline or myoclonus. The rationale for trialling opioid rotation was the potential to improve symptoms by reducing the concentration of accumulated toxic metabolites. The mean reduction in pain following rotation was 0.8 points on a visual analogue scale (from 4.4 to 3.6 points) and the mean reduction in daily oral morphine equivalents was 241 mg, both of which were statistically significant.

The most recent Cochrane review assessing opioid rotation was published in 2004.[21] No RCTs were available for inclusion. The authors concluded that although opioid rotation may be the only option for symptomatic relief for patients with refractory cancer pain, the evidence is based on a combination of anecdote and uncontrolled studies.

Multiple systematic reviews on opioid rotation have been published since the Cochrane review.[22,23] They cautiously suggest opioid rotation as an option for refractory cancer pain while acknowledging the absence of prospective RCT evidence.

There are still no prospective, placebo-controlled trials to guide clinical practice. The only available prospective studies compared opioid rotation with different opioids or other options for refractory pain, but not with a placebo control.[22,23] In a randomised study of 50 participants with persistent pain who were taking at least 100 mg of oral morphine equivalents per day, participants were randomised to either rotation to transdermal fentanyl or a combination of 50% of the fentanyl dose that the other group received plus regular oral oxycodone.[24] Each group had a statistically significant improvement in pain scores.

Authors' opinion: opioid rotation is less relevant in modern practice when many patients receive a combination of different opioids to optimise their pain control. It is likely, however, that certain opioids are more suited to individuals than others on the basis of multiple factors (e.g. preference, route of delivery, cost, convenience). It is

common practice in palliative care to rotate to a different opioid if there is a perceived lack of efficacy or signs of opioid toxicity. Dose reduction should be considered when doing so and palliative specialist advice sought if there is any uncertainty.

Ketamine

Ketamine is a phencyclidine derivative used primarily as an anaesthetic agent.[25] It acts principally as an N-methyl-D-aspartate receptor antagonist. It is often used in perioperative and chronic nonmalignant pain and the approach has been extrapolated to those with malignant pain. Ketamine for palliative cancer pain management continues to inspire a great deal of controversy.

In an Australian RCT of 185 palliative patients with advanced cancer, subcutaneous ketamine infusion was no better than placebo when used in a dose-escalating regimen over five days.[26] The doses achieved were consistent with clinical practice and the population under study had the characteristics of those in a palliative care practice. Another multicentre RCT of 214 patients with cancer-related neuropathic pain showed ketamine was equivalent to placebo.[27]

Two smaller RCTs also did not demonstrate benefit of ketamine compared with placebo in patients with advanced cancer.[28,29] Ketamine was better than placebo in one small, single-institution study of 10 patients.[30] This study assessed pain scores every 30 minutes for a total of only three hours. No rescue analgesia was given. Thus, the only RCT showing a benefit was both very small and least resembled the actual use of ketamine in clinical practice. Despite this, a Cochrane review claims insufficient evidence to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of refractory cancer pain.[31]

Case series and observational studies continue to be published. One recent case series of 47 patients with refractory cancer-related pain treated with subanaesthetic ketamine in an ambulatory context showed improvement from baseline pain levels.[32]

Separately, a retrospective cohort study of 70 patients measured a mean pain score improvement from 7.0 to 4.0 on the numerical rating scale.[33] The median opioid dose reduction was 25.5% and patients needed to be taking more than 300 mg oral morphine equivalent per day to be eligible. The authors posited there may be an unidentified 'good responder' group to account for the discrepancy from the RCTs.

The question is whether the positive cohort studies and case series outweigh the negative, large RCTs. Further observational studies will not provide that information.[34]

Authors' opinion: the use of ketamine for chronic cancer pain is not supported by the existing evidence.

Medicinal cannabis

Medicinal cannabis is sometimes prescribed for cancer pain management. Tetrahydrocannabinol (THC) and cannabidiol (CBD) are generally accepted as the clinically relevant compounds. However, some claim this ignores the so-called entourage effect, whereby the combination of multiple cannabinoids plus terpenes found in the cannabis plant act together to provide the desired effect.[35] THC is a partial agonist of CB1 and CB2 receptors. CBD is a negative allosteric modulator of CB1 receptor and may act on other receptors.[36] If medicinal cannabis has a role in cancer pain, the pathophysiological explanation remains elusive. Early studies were suggestive of an antinociceptive effect.[37,38] The results of modern, higher-quality studies have been mixed.

A two-week, parallel-group trial of 177 patients comparing THC:CBD extract, THC extract and placebo found a statistically significant change from baseline in mean pain numerical rating scale scores in favour of the THC:CBD extract compared with placebo (improvement of –1.37 *vs* –0.69).[39] Medication doses were determined by self-titration. Breakthrough opioid use was similar across the three groups. A similarly large study showed a reduction in average daily pain score with use of nabiximols (a specific THC:CBD 1:1 extract) compared with placebo.[40]

In contrast, both an RCT of 399 patients and a withdrawal design RCT of 406 patients failed to demonstrate that the use of nabiximols was superior to placebo.[41] The results of an RCT of 380 participants were similarly contradictory.[42] So too was a smaller pilot RCT in 16 patients investigating nabiximols for the treatment of chemotherapy-induced peripheral neuropathy.[43]

A 2021 systematic review and meta-analysis of RCTs concluded that there was moderate to high certainty that medicinal cannabis provides a small or very small improvement in pain relief in patients with chronic pain.[44] Another recent meta-analysis showed no benefit of medicinal cannabis for pain in adults with advanced cancer.[45]

Authors' opinion: medicinal cannabis may provide a small benefit in cancer pain for some adults. The clinical significance of this is uncertain. Given the lack of high-quality evidence of clinical benefit it is hard to recommend medicinal cannabis as standard practice for cancer pain management.

Conclusion

RCTs provide the highest level of evidence when assessing the efficacy of a drug or intervention. RCTs in patients receiving palliative care, although demonstrably possible, are difficult to orchestrate, in part due to the unique population characteristics leading to significant attrition. Many controversial issues in palliative care are difficult to resolve. Other pain management options not covered in this article include lignocaine infusion, clonidine and NSAIDs or corticosteroids alone or in combination with opioids. Evidence-based care should be prioritised in this specialty as much as in others. **PMT**

References

A list of references is included in the online version of this article (www.painmanagementtoday.com.au).

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