Safe and effective use of opioids in patients with advanced cancer

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Practical aspects of prescribing opioids for patients with cancer include selecting an initial opioid, switching opioids when analgesia is inadequate and overcoming barriers to opioid use such as patient concern about addiction and reduced life expectancy. It is also important to address the contribution of distress to pain and to recognise the limitations of opioids, such as opioid-induced hyperalgesia.

Key points

- **Opioids are first-line therapy for the management of moderate-to-severe cancer-related pain and are also used to treat refractory breathlessness and cough in palliative care.**
- **There is no difference in the analgesic and side-effect profile of the commonly used opioids, and choice of agent should take into consideration the convenience of dosing, flexibility to respond to pain and risk of renal or hepatic impairment.**
- **Patients respond to opioid analgesia differently because of genetic variation in mu opioid receptors, and switching to another opioid should be considered if analgesia is inadequate or significant side effects develop.**
- **Opioids may be used via different routes of administration, with subcutaneous and transdermal opioids indicated for patients whose condition is deteriorating and who are unable to swallow.**
- **The experience of pain is mediated by psychological and existential distress, and failure to recognise distress may lead to inappropriate opioid use and risk of toxicity.**
- **The fear of shortened life expectancy and addiction are common barriers to opioid use for both patients and physicians.**

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Opioids are used frequently as part of management for patients with cancer-related pain and in palliative care. This article addresses some practical aspects of prescribing opioids relevant for GPs and specialists, along with the limitations of opioids and barriers to their use.

Why are opioids used for patients with cancer?

Pain is a common and feared complication of cancer, affecting up to 50% of patients receiving active treatment for cancer and 80% of those with advanced cancer.[1,2] The WHO analgesic ladder is a structured approach to the selection of analgesia for cancer-related pain (Figure 1).[3] Adequate pain control can be achieved by following this approach in 70 to 90% of patients.[4] Opioids are first-line therapy for moderate-to-severe pain related to cancer.[5]

Breathlessness is another indication for opioids, with approximately 60% of patients with refractory breathlessness responding to morphine.[6] Additionally, opioids are effective for the management of cough, which affects up to 40% of patients with advanced

cancer.[7] Opioids, particularly codeine and loperamide, may also be indicated for the management of diarrhoea in some circumstances.[4]

Which opioid should be used?

Multiple studies have consistently shown no significant differences in the analgesic or adverse effects between the commonly used opioids morphine, oxycodone and hydromorphone.[4,8-11] The choice of agent should take into account the convenience of dosing, flexibility to respond to pain and risk of renal or hepatic impairment. The significant genetic variation in the metabolism of codeine leads to unpredictable analgesic effects and risk of side effects, and therefore it is not favoured in the management of cancer pain.[5]

Transdermal fentanyl and buprenorphine are convenient options, with a reduced pill burden, but dose titration is more challenging because of the delayed effect of dose changes caused by accumulation of the drug within skin tissue. The delay in achieving maximum serum concentrations after a dose increase and in reducing serum concentrations after a decrease can predispose to periods of poorly controlled pain or risk of opioid toxicity, respectively.[12] The fixed doses of transdermal patches also limit the ability to modify the dose compared with oral or injectable preparations.

Methadone is a more challenging opioid to use, with an unpredictable half-life and variable pharmacokinetics. Its use in treatment of cancer pain should therefore be reserved for pain and palliative care specialists.[5,8]

Tapentadol, with its combined opioid and noradrenergic reuptake inhibitor actions, is a newer agent. Several studies have demonstrated its efficacy in the management of moderate-to-severe malignant pain in opioid-naïve patients.[13,14] Clinical experience using tapentadol for patients with cancer-related pain is, however, limited.

Renal impairment is four times more common among patients with cancer than in the general population.[15] This estimate excludes patients with myeloma, among whom renal impairment is even more common. Opioids and their metabolites can accumulate in patients with renal impairment, increasing the risk of opioid toxicity and delirium, which can easily be mistaken for irreversible terminal decline in patients with advanced malignancy.[15] In patients with renal impairment, hydromorphone is likely to be associated with fewer adverse effects, and fentanyl, buprenorphine and methadone are considered safe.[15]

Hepatic impairment is also common in cancer patients. The liver is involved in the metabolism of many opioids, and some will be affected by the reduction in first-pass metabolism, leading to increased oral bioavailability. In the case of combination oxycodone–naloxone (Targin), the increased bioavailability of the naloxone component reduces the analgesic effect of the oxycodone component in patients with hepatic impairment. Also in patients with hepatic impairment, the dosing frequency of morphine and hydromorphone should be reduced, but fentanyl is considered safe.[16]

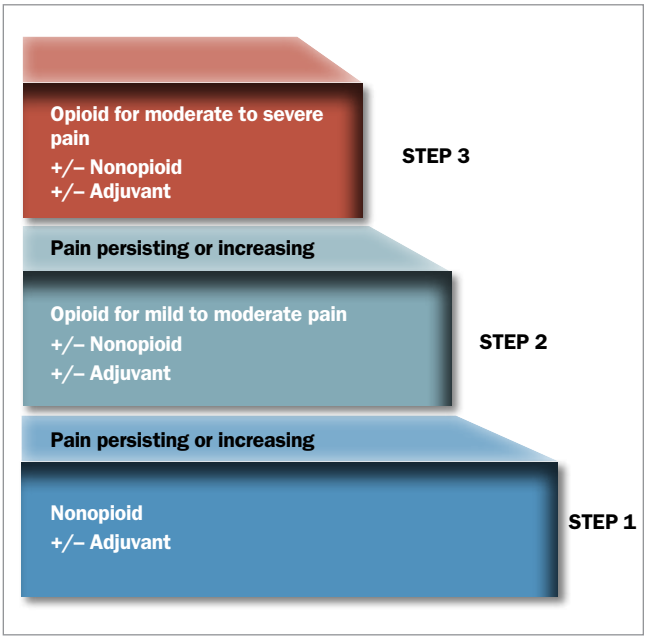


Figure 1. Structured approach to the selection of analgesia for cancer-related pain (WHO's pain relief ladder).[3]

Reproduced with permission from: World Health Organization. WHO's cancer pain ladder for adults. Available online at: http://www.who.int/cancer/palliative/painladder/en/ (accessed September 2016).[3] © WHO 2016.

What is the rationale for opioid switching?

Opioid analgesics act through binding to mu opioid receptors.[17] There is significant genetic variation within the population, leading to numerous subtypes of mu receptors. This accounts for the varied response to different opioids among patients.[5] Opioid switching may be considered for patients who develop side effects before achieving adequate pain relief with one opioid, but who may respond to a different opioid with improved pain control and fewer side effects. The choice of second opioid is empirical as there is no way to predict individual response, and more than one opioid may need to be trialled. Although there is no firm evidence supporting this practice, it is a well-established strategy based on expert opinion and observational studies.[18]

The principle of equianalgesic opioid doses underpins the practice of opioid switching. The equianalgesic dose of an opioid is that which produces the equivalent analgesic effect to the reference compound, oral morphine (Table).[19,20] When switching between opioids, it is usual and safe to reduce the calculated dose of the new opioid by 25 to 50% to account for incomplete cross tolerance between opioids. Additionally, the effects of renal and hepatic dysfunction should be considered.[19] Tapentadol represents a challenge in regard to opioid switching as its analgesic equivalent dose is substantially less than its opioid equivalent dose because of its noradrenergic action.[21] Given the significant interindividual variability in response to different opioids, it is important that patients are monitored carefully during the process of opioid rotation

Table. Equianalgesic doses of opioids*

Oral opioids		
Opioid	**Conversion factor (factor x morphine dose = equianalgesic opioid dose)**	**Equianalgesic opioid dose†**
Morphine		10 mg
Hydromorphone	0.2	2 mg
Oxycodone	0.67	5 to 7.5 mg
Tapentadol	3	50 mg‡
Tramadol	5	50 mg
Codeine	8	75 to 90 mg
Transdermal opioids		
Opioid	**Patch strength**	**Equianalgesic oral morphine dose**
Buprenorphine (transdermal)	5 µg/h patch, applied once weekly	12 mg over 24 h
Fentanyl (transdermal)	12 µg/h patch, applied every 3 days	35 to 40 mg over 24 h

* Adapted from Western Australia Cancer and Palliative Care Network *Opioid conversion guide*.[20]
† Opioid dose equivalent to 10 mg oral morphine.
‡ Tapentadol equianalgesic dose has been rounded to the nearest available tablet dose.

and dose titration to minimise the risk of complications. Specialist guidance should be sought to assist with opioid rotation.

Rotation to methadone is sometimes considered for patients with ongoing poorly controlled pain and opioid-related side effects despite trials of different opioids. Given the unpredictability of methadone's pharmacokinetics and uncertainty of the equianalgesic dose, rotating to methadone should always be done with specialist support, with consideration given to hospital or hospice admission for the duration of the rotation to ensure patient safety.

Opioids may also be used in combination to improve analgesia while limiting side effects through the selection of opioids that together have less effect on the mu receptor than the equivalent dose of either one alone.[22] The combination of opioids in subtherapeutic doses has been shown in laboratory studies to produce analgesic synergy (increased analgesia compared with the equianalgesic dose of either opioid independently), while the decreased effect on the mu receptors reduces side effects such as nausea and constipation. Methadone, because of its action on both opioid and nonopioid receptors including the N-methyl-D-aspartate (NMDA) receptor, is increasingly used as an 'adjuvant' analgesic in combination with another opioid, with a possible synergism of the analgesic effect between methadone and other opioids.[23-25]

What is the preferred mode of administration: oral, parenteral or transdermal?

For most ambulant patients, it is appropriate to commence opioid therapy with an oral agent. Although the tradition in palliative care has been to commence opioids using a regular or as-required short-acting opioid and then to adjust to a slow-release preparation once the opioid requirement has been ascertained, it may be more convenient or appropriate to commence treatment with a slow-release agent, with use of a short-acting opioid for breakthrough pain.

Subcutaneous administration leads to a faster onset of action than oral administration, so may be preferred when rapid pain control is necessary. It may also be preferred when the patient has significant constipation, which may affect the use of controlled-release oral preparations.

Additionally, subcutaneous or transdermal opioids are indicated for patients whose condition is deteriorating and who are unable to swallow. Multiple studies have demonstrated no difference in pain relief, quality of life or adverse effects between subcutaneous and intravenous opioids. The increased safety, greater accessibility in community and hospice settings and less invasive nature of subcutaneous administration make it preferred to intravenous administration in palliative care.[26]

The absorption of transdermal opioids is reduced in cachectic patients, who may require higher doses. Transdermal administration may also be affected by other common cancer symptoms, including sweating, which can reduce patch adhesion and hence drug absorption, and fever, which can increase absorption and hence the risk of opioid toxicity.[26] Transdermal opioids can, however, be very convenient for patients who are unable to take oral medications or find compliance difficult.

About 5 to 15% of cancer patients do not achieve adequate pain control with systemic opioids or experience intolerable side effects. Some of these patients may benefit from intrathecal or epidural opioid administration. Intrathecal administration enables the use of much lower opioid doses, often in combination with other agents such as a local anaesthetic or clonidine, which have further opioid-sparing benefits.[27]

What are the limitations of opioids for cancer pain?

Although opioid dosing is based on efficacy rather than a predetermined dose range or ceiling, the development of side effects may be dose-limiting.[4,17] Opioids are effective in the management of all types of cancer pain, but do not have the same efficacy for all types.[17] Neuropathic pain, which affects over a third of cancer patients, is often considered poorly responsive to opioids.[28] Nevertheless, opioid analgesia alone can be effective for neuropathic pain, although the combination of an opioid with adjuvant analgesia (such as pregabalin, gabapentin or nortriptyline) has been shown to be associated with improved pain control, fewer side effects and lower opioid doses.[28]

Opioid-induced hyperalgesia (OIH) is a paradoxical increase in pain associated with increasing or high doses of opioids.[4] Clinically, OIH can be challenging to identify among patients with cancer-related pain, in whom increasing opioid doses may relate to cancer progression or complications.[29] OIH differs from tolerance, in which an increasing opioid dose is needed to achieve the same effect. Features that can help differentiate OIH from cancer progression or opioid tolerance include the following.[30]

- Pain associated with cancer progression or opioid tolerance responds to increasing opioid doses, whereas the pain associated with OIH continues to increase despite an increase in the opioid analgesic dose.
- Pain in OIH may be felt in different areas of the body and may have a different quality to the initial pain for which the analgesia was commenced.
- Pain in OIH may be associated with allodynia (where non-noxious stimuli are perceived as painful), hyperalgesia (the experience of disproportionately severe pain following a non-severe noxious stimulus) and myoclonus.

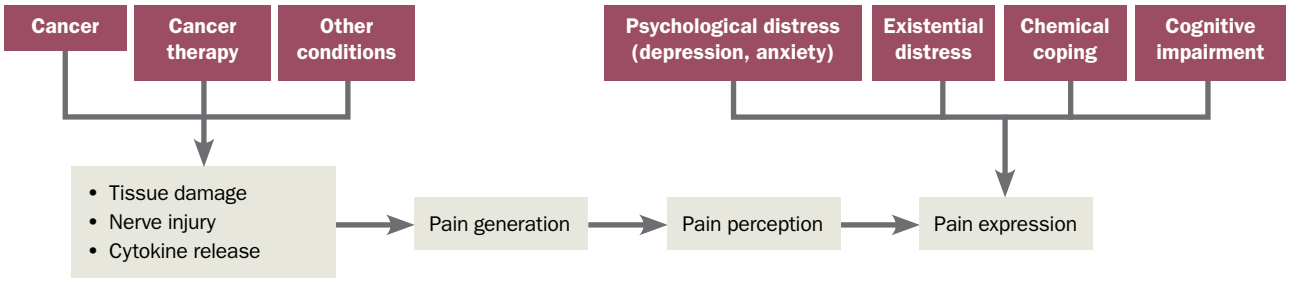
The mechanism of OIH is likely related to central sensitisation, in which opioid binding leads to glial cell activation within the nervous system and a change in the balance between facilitatory and antinociceptive pathways.[4] The incidence of OIH among patients with cancer-related pain is not well established.[30] Opioid dose reduction or opioid rotation, the addition of or rotation to methadone because of its action at the NMDA receptor, and the use of nonopioid adjuvant analgesics are all strategies used in the management of OIH.[4,30]

The term 'total pain' describes the interaction between the physical, psychological and existential distress of patients facing a life-threatening illness (flow chart). Pain often occurs in the context of psychological and existential distress, and poorly controlled pain and psychological distress contribute significantly to suffering.[1] Patients may use opioids to manage distress and anxiety, not recognising the contribution of distress to pain.[29] Opioids are, however, ineffective for the management of distress and expose patients to the risks of opioid toxicity, delirium and accidental overdose, along with ongoing psychological suffering. As such, it is essential that thorough pain assessments include the psychological and social context of patients, so that distress can be recognised and managed appropriately.

What are the barriers to opioid use?

Fears regarding opioids are well recognised as barriers to patients achieving adequate pain control. These fears include concerns

Factors that may contribute to total pain in patients with cancer*



* Adapted from Hui and Bruera. J Clin Oncol 2014; 32: 1640-1646.[1]

about side effects, which distract health professionals from dealing with the cancer, the development of addiction and the view of morphine as 'the last resort'.[31,32] In one group of patients studied, up to 30 to 40% believed opioids shorten life expectancy.[33] As a consequence of such fears, patients may under-report pain, leading to increased symptoms and poor quality of life.[34] Several studies have demonstrated no correlation between opioids used appropriately in palliative care and survival.[35]

Both patients and physicians report fear of addiction as a barrier to opioid use.[36] Physical dependence, where cessation of the medication leads to withdrawal symptoms, and tolerance, where dose escalation may be required to accommodate reduced sensitivity to the effect of the drug, develop in all patients who use opioids long term.[17] However, addiction refers to the compulsive, uncontrolled and harmful use of a substance.[4]

The risk of opioid addiction for most patients receiving long-term opioid therapy for pain is estimated to be approximately 10% but is presumably lower in palliative care because of the short duration of exposure.[37] Nevertheless, patients should be educated about the differences between addiction, dependence and tolerance. The risk of opioid addiction is substantially increased among patients with a prior history of substance, alcohol or tobacco misuse, all of which are risk factors for some cancers. Additionally, mental health disorders such as anxiety, depression, personality disorders and post-traumatic stress disorder, all of which may be exacerbated by a diagnosis of cancer, are also associated with an increased risk of addiction.[29]

The effects of long-term opioid use are now better understood from experience in the management of patients with chronic noncancer pain. They include hypogonadism, osteoporosis and sleep-disordered breathing.[36] Although the effects of long-term opioid use for cancer-related pain are not well studied, they are likely to become more important as patients with metastatic malignancies live longer. Up to 5 to 10% of long-term cancer survivors continue to experience pain long after completing their treatment.[38]

All patients, including those with substance misuse problems, deserve adequate management of cancer pain. For most patients, aberrant opioid use and the long-term complications of opioid use are unlikely to be problems. However, these are important areas for ongoing consideration and research, given our increasing awareness of prescription opioid misuse in the community and the improved survival times for some cancers. It is extremely important to consider pain in its entirety, including the social, psychological and spiritual factors contributing to pain as well as the physical factors. Strategies that should be considered for patients at risk of opioid misuse and those likely to require long-term pain management include staged supply of opioid medications, maximisation of nonopioid adjuvant analgesia, nonpharmacological pain management techniques and the early engagement of specialist palliative or pain management multi-disciplinary teams.

Conclusion

Pain is a common complication of advanced cancer that is feared by patients and, if not well managed, is associated with poor quality of life, functional impairment and increased distress. Opioids can be very effective as part of the management of patients with cancer pain. Genetic variation in mu opioid receptors accounts for the variability between patients in response to different opioid analgesics and underpins the practice of opioid switching in patients with inadequately controlled pain or opioid-related side effects.

Patients may express concerns regarding opioid analgesia, including the risk of side effects, reduced life expectancy and addiction. These concerns should be explored and discussed with patients. It is extremely important to assess psychological, social and existential distress in the investigation of patients with cancer pain as, without attention to this distress, good pain control is unlikely. PMT

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

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