The role of opioid analgesia in treating chronic pain

This article reviews clinically relevant aspects of selected opioids, their action, and current consensus regarding opioid prescribing. Chronic pain is an extremely common condition estimated to affect between one third and one half of all UK citizens, a statistic that will only increase as the population ages (Fayaz et al, 2016).

Definition of opioid

Opioid is a general term used to describe naturally occurring, semi-synthetic and synthetic drugs that bind to opioid receptors producing physiological analgesia.

Opioid receptors

Pain perception is modulated by multiple systems including endogenous opioid system. The existence of at least three opioid receptor types, referred to as mu (μ), kappa, and delta, is well established (*Table 1* outlines the locations of specific receptors).

The mu opioid receptor is the most relevant opioid receptor in mediating analgesia (Peckys and Landwehrmeyer, 1999). Mu opioid receptors are critically important for development of biomarkers of pain conditions and their responses to treatment (Peciña et al, 2015). There is considerable inter-individual variability in response to opioids. This requires careful monitoring of titration to desired effect.

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Table 1. Opioid receptor activity*

Receptor	Analgesic effect and area of activity	Side effects	Location within CNS with highest receptor density	Stimulated by input from
Mu	Most profound analgesic effects of opioids, supraspinal and spinal analgesia	Bradycardia, sedation, euphoria, physical dependence, respiratory depression, miosis	Mu opioid receptors are widely distributed in the brain. The highest levels are in the thalamus and in the limbic system and basal ganglia, including the amygdala, nucleus accumbens, anterior cingulate cortex, and substantia gelatinosa in the dorsal horn of the spinal cord	Mechanical, chemical and thermal stimuli
Kappa	■ Spinal analgesia ■ Supraspinal analgesia	Less respiratory depression, constipation, sedation	CNS: striatum, thalamus, hypothalamus, cerebral cortex, cerebellum and brainstem areas, spinal cord	Thermal stimuli and visceral pain
Delta	■ Spinal analgesia ■ Supraspinal analgesia	Respiratory depression	CNS: cerebral cortex	Mechanical stimuli and inflammatory pain

**Opioid classification is determined by mu receptor activity. Classes include full agonists, partial agonists, agonist-antagonists and antagonists*

Individual variation of pain perception is attributed to variability of mu opioid receptor expression and responses to different opioids. Mu opioid receptors are encoded by the mu-opioid receptor gene (OPRM1). Variation of functional single nucleotide polymorphism in OPRM1 changes the effect of endogenous opioid release after sustained painful stimulus on dopamine release at the nucleus accumbens. In individuals with the A118G polymorphism, this release is blunted. These individuals also show lower placebo response activation as well as higher neuroticism scores (Peciña et al, 2015).

Opioid classification

Opioid classification can be determined by mu opioid receptor activity. Classes include full agonists, partial agonists, agonist-antagonists and antagonists (*Table 2*). Opioid agonists like morphine bind to opioid mu receptors and this causes analgesia, but also causes undesirable side effects such as respiratory depression and constipation.

Opioid therapy selection

The clinical use of opioids requires knowledge of drug selection, route of administration, guideline dosage recommendations, and potential adverse side effects. Short-acting opioids should be used, since long-acting formulations carry more risk (Ray et al, 2016). Some conditions require a combination of short- and long-acting formulations (*Table 3*).

Other factors to consider include the patient's preferences and past opioid history and the nature and severity of the condition. The patient's specific risk factors such as age, hepatic and renal impairment, medical comorbidities and other medications that could increase their vulnerability to adverse effects of opioids.

Opioid therapy for cancer pain

The World Health Organization pain ladder for cancer pain is still widely used despite being over 30 years old (World Health Organization, 1996) (*Figure 1*). It is

Table 2. Activity of selected agents on mu receptor

Opioid response	Action	Example
Full agonist	Activate mu receptors, producing analgesia	Morphine, fentanyl, oxycodone, hydrocodone, methadone
Partial agonist	Has a strong affinity for mu receptors, but produces mild analgesia that is accompanied by an analgesic ceiling effect	Buprenorphine
Agonist-antagonist	Act as antagonists on mu receptors and as agonists on kappa receptors leading to milder analgesic effects with fewer adverse effects	Pentazocine, butorphanol, nalbuphine
Antagonist	No analgesic effect; reverses effects of opioid agonists, provokes opioid withdrawal	Naloxone, naltrexone

based upon the relationship between pain intensity and increasing opioid strengths with recommendations for combining opioids with non-opioids including adjuvant therapies (Caraceni et al, 2012).

Selecting the opioid therapy in cancer pain

Keep administration simple: oral or transdermal. Obtain any history of previous opioid use and the patient's preferences. The mechanism of pain does not predict the response to a particular opioid. Use an appropriate dose of an opioid, based on the patient's preferences and the patient's reported pain relief, balanced with decreased adverse effects. Start a single opioid rather than a combination of multiple opioids if possible. Short-acting opioids are appropriate for immediate pain relief. Long-acting opioids are recommended for chronic moderate to severe cancer pain and can be instituted as the patient's opioid requirements increase.

Provide rescue ('breakthrough') medications instead of increasing the scheduled doses to prevent overmedication. For uncontrolled pain plan to gradually increase opioid dose. Educate the patient about likely side effects and seek to manage them preventatively, i.e. prevent opioid-induced constipation by starting a bowel regimen. Expect to rotate opioids if one opioid shows poor response. Regularly assess the patient and re-evaluate the treatment plan if inadequate relief or adverse side effects arise.

Morphine is the opioid of first choice and gold standard for moderate to severe cancer pain. The optimal route of morphine administration is by mouth. Short-acting formulations of morphine have a rapid effects and pain relief expected for 4 hours. The simplest method of titration is to given immediate release morphine 5–15 mg every 4 hours and the same dose for breakthrough pain and the total dose of morphine should be reviewed daily. Once you calculate the needed dose, plan to replace some of the immediate release with long-acting extended release morphine every 12–24 hours. The patient should still have immediate release morphine for breakthrough pain available every 4 hours. Do not make extended release morphine changes more frequently than every 48 hours. The goal of effective opioid therapy in chronic pain is to provide analgesia and improved function over a regular time period. The main challenge of opioid therapy is maintaining ongoing effectiveness and managing intolerable side effects.

Older patients (>60 years old) have reduced distribution volumes and reduced clearance. Patients with renal impairment may accumulate toxic metabolites of morphine, morphine-3-glucuronide and morphine-6-glucuronide, and should be given reduced doses or switched to another opioid (Niscola et al, 2010). For patients who are unable to take oral morphine, the alternative is subcutaneous morphine at a ratio of 1:2–1:3 oral to subcutaneous.

Table 3. Pharmacokinetics of selected opioids

Opioid	Dosing and frequency	Time to maximum plasma concentration (Tmax)	Adverse effects
Buprenorphine	Transdermal 5 μg/hr every 7 days	72 hours	Dizziness, nausea
Codeine	15–60 mg every 6 hours	1.5 hours	
Fentanyl	Transdermal 12 μg/hr every 72 hours	27–38 hours	Nausea, vomiting*
Hydrocodone	5–10 mg every 4–6 hours	1.3 hours	Drowsiness, nausea, dizziness
Hydromorphone	2–4 mg every 4–6 hours	1 hours	
Methadone	5 mg twice a day	2.5–4 hours	Nausea, vomiting†
Morphine IR	5–30 mg every 4 hours	1.2 hours	Constipation
Morphine ER	15–30 every 12 hours	2.3–9.5 hours	Constipation
Oxycodone IR	5–10 mg every 4 hours	1.5 hours	Drowsiness, nausea
Oxycodone CR	5–10 mg every 12 hours	3.2 hours	Constipation, nausea, drowsiness
Oxymorphone	5–10 mg every 4 hours	2 hours	
Tramadol	50–100 mg every 4 hours	2 hours	Dizziness, irritability, seizure ‡

**Transdermal fentanyl has delayed onset of up to 12–24 hours. †Methadone has a non-linear potency curve. ‡Tramadol has a maximum dosage of 400 mg/day. CR = controlled release; ER = extended release; IR = immediate release.*

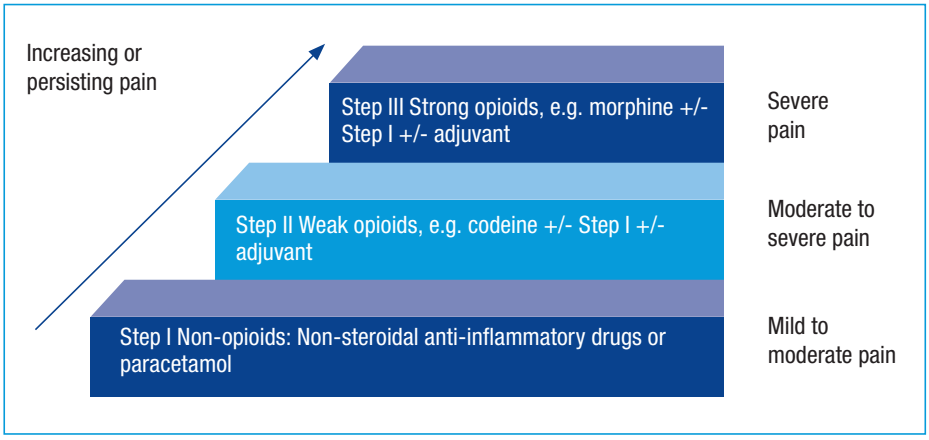


Figure 1. World Health Organization analgesic ladder. Adapted from World Health Organization (1996).

Selecting opioid therapy in cancer pain

Many alternative full-agonist opioids are available as morphine alternatives, including oxycodone, hydromorphone, and oxymorphone, which are all available in short- and long-acting forms. Transdermal fentanyl is a highly potent non-oral option for pain treatment; it should not be prescribed for opioid-naïve patients and needs to be cautiously titrated. Methadone is useful because of its long, although variable, half-life. Its potency increases in a non-linear fashion as the dose increases so should be managed by providers with special training and experience.

Several opioid medications are notable for having at least theoretically less risk associated with their administration. Tramadol is a very mild opioid analgesic with good effect on neuropathic pain because of its serotonin and noradrenaline reuptake effect. It has a dosing ceiling of 300–400 mg/day a day because of the risk of causing seizures. Buprenorphine is used for both pain and for opioid use disorder treatment. Buprenorphine is a mixed agonist-antagonist and therefore may have a ceiling effect, which reduces the maximum effective dose but may also reduce the incidence of adverse effects, especially respiratory suppression. This medication can be prescribed sublingually with naltrexone for opioid use disorder or without for pain. It is also available in a long-acting transdermal form for chronic pain. It is important not to start buprenorphine while the patient is taking other chronic opioids, as it can cause acute opioid withdrawal symptoms.

In patients with significant renal failure, hydromorphone and morphine are both relatively contraindicated because of the risk of accumulation of renally excreted toxic metabolites. In renal and hepatic impairment, methadone and fentanyl are less likely to cause adverse effects resulting from accumulation of metabolites, although any sedating medication raises the risk of encephalopathy.

Opioids for non-cancer pain

Numerous studies have shown that while opioids are very effective for many forms of acute pain, their usefulness in chronic pain conditions over 3 months is unclear. Especially at high doses, opioids cause many adverse health consequences which can worsen as the daily dose increases. In some conditions such as fibromyalgia, chronic headache and mechanical back pain, chronic opioids do not appear to confer any benefit. Overall, the benefits of long-term opioid therapy appear limited and uncertain, while there is a clear dose-dependent risk of harm to the patient (Chou et al, 2015).

Chronic opioid therapy for non-cancer pain in the past more closely paralleled prescribing practices for cancer pain, and many patients were managed using long-acting opioids combined with short-acting opioids for breakthrough pain. Several considerations have changed this: first, that tapering long-acting opioids is usually more difficult than with short-acting forms, and second, that long-acting opioids appear to have greater morbidity and mortality associated with them (Ray et al, 2016).

As needed dosing allows the patient to use opioid pain relievers tactically, for example to facilitate exercise or spending time outdoors with family. There have been concerns raised about the potential for as needed dosing of opioids to reinforce the patient's anxiety related to fluctuations in pain intensity, and to reinforce pain behaviour. In practice, many patients prescribed as needed medications will fall into a routine of using them all at specific times throughout the day, so that they are really on a self-imposed fixed schedule. Therefore, combining scheduled opioids with as needed medication for breakthrough pain is not recommended for non-cancer pain.

Chronic opioids have many side effects and risks of morbidity and mortality, which worsen with additional comorbid medical and psychiatric conditions. There are numerous pharmacological and other treatments for chronic pain, and any specific treatment is unlikely to be effective for more than a minority of pain patients (Moore et al, 2013). Chronic opioids should be started with the understanding that they will be reduced or stopped if the patient does not appear to benefit or is having significant adverse reactions (see *Table 4* for common adverse effects of opioids). Since opioid tolerance develops quickly, it is important to discuss this up front with the patient and to let him/her know that the dose will not be escalated.

The guidelines for safe opioid dosing have changed dramatically over the past 20 years, from guidance that there 'is no ceiling effect' for opioids, to specific recommendations based on morphine equivalents per day. The threshold for concern, expressed in morphine equivalents daily, has steadily decreased, with early recommendations for no more than 180 morphine equivalents, then 120 morphine equivalents, and the Centers for Disease Control in the United States currently advocating keeping the daily dose below 50 morphine equivalents and not increasing it above 90 morphine equivalents, based on mortality and morbidity data (Centers for Disease Control, 2016). 50 morphine equivalents corresponds to 50 mg/day of morphine, 30 mg/day of oxycodone or 12 mg/day of methadone.

Patients with comorbid psychiatric disorders or substance use disorders or a family history of substance use disorder are at much higher risk of developing addiction or misuse with chronic opioid therapy. The risk of respiratory suppression increases greatly when opioids are taken with alcohol, benzodiazepines or other sedatives, or in patients with sleep apnoea. These issues may develop or emerge during the course of treatment so that periodic reassessment is

Table 4. Most common adverse effects of opioids

Side effect	Frequency with oral long-acting opioids	Does symptom diminish with tolerance?	Notes
Constipation	Very common	No	Most common side effect, related to decreased gastric and intestinal motility
Nausea or vomiting	Common	Yes	Transient, 2–3 days, both decrease gastric motility and brainstem medullary chemoreceptor zone activation
Sedation	Common	Yes	Usually temporary
Cognitive impairment	Occasional	Yes	
Pruritus	Occasional	Yes	Related to histamine release, common with intravenous administration
Dysphoria	Occasional	Yes	
Respiratory depression	Rare	Yes	
Addiction	Variable	No	

necessary. Assessment with the Opioid Risk Tool can be helpful to identify higher-risk patients (Passik et al, 2008).

Monitoring chronic opioid patients

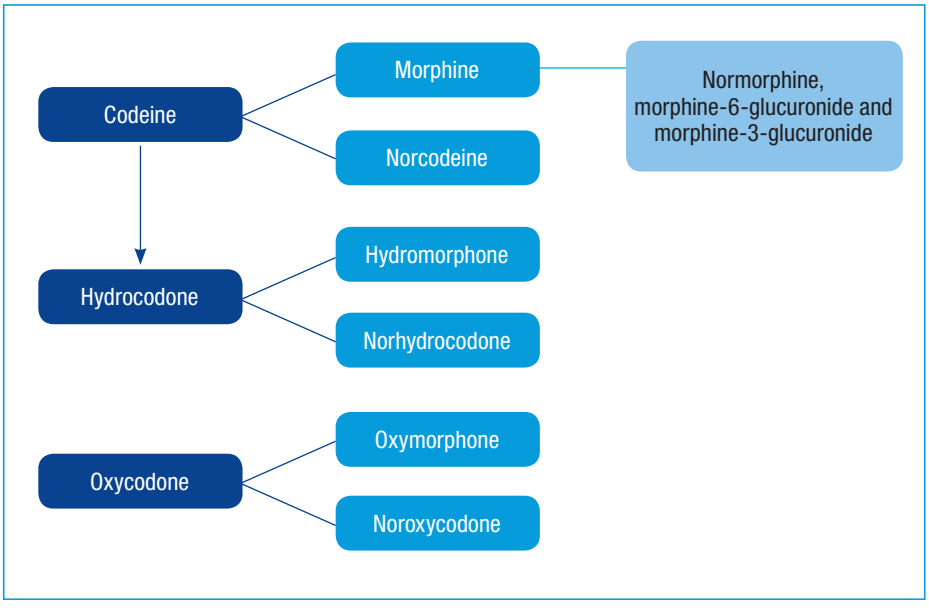
Chronic opioid therapy should only be provided with structured monitoring of patients for treatment progress and to watch for aberrancies and adverse effects. Identifying concrete functional goals is important to judging the success of opioid therapy; do not settle for vague status reports or improvements of pain intensity. Assessments of compliance such as pill counts and urine drug screens can help identify patients who are overusing their medication, using other drugs, and those who may be diverting their opioid prescriptions. Knowledge of opioid metabolism is necessary to interpret urine drug screen results (*Figure 2*). If patients have abnormalities on any of these assessments, they must be documented and a decision made whether these aberrancies require increased surveillance, or whether prescribing should be stopped entirely.

Exit strategies for chronic opioid therapy

Patients at high risk of substance use disorders are more likely to have aberrancies during opioid treatment, regardless of the dose or adequacy of pain treatment. Many aberrant behaviours observed in opioid patients may provide early warning of opioid misuse or addiction. Repeated aberrancy or high-risk aberrancies such as doctor shopping, buying or selling opioids, or prescription tampering require the patient to be taken off opioids. This process is rarely easy for patient or provider, but is better accepted if this possibility has been explicitly discussed earlier. If the patient is simply not benefitting from opioids or is showing repeated milder aberrancies, a gradual taper of 10% a month is typically well tolerated. This can be accelerated to weekly prescriptions with weekly decreases in more urgent cases.

If the patient poses a safety risk to him-/herself or others as a result of overdose or diversion, it is sometimes necessary to simply discontinue prescribing opioids entirely. In this case, it is useful to offer other pain treatments as well as treatments for withdrawal symptoms. If this determination is made shortly after a visit, such as may happen if the patient's urine drug screen comes back positive for metabolites of heroin or other drugs of abuse, the patient may be notified of this immediately rather than waiting for the next visit, and counselled on how he/she can self-taper with what remains of his/her current opioid prescription. In any case, the abnormal findings, plan of action, and treatment rationale should be clearly documented for future reference. A retrospective study of pain prescribing after aberrancy in primary care has found that many providers simply document the issues and continue to prescribe as before, an unsafe treatment strategy (Gupta et al, 2011).

Figure 2. Examples of the metabolism of opioids. Fentanyl, methadone and oxymorphone do not metabolize to other opioid analgesics.



KEY POINTS

- Opioids are currently evidence based for the treatment of chronic cancer pain.
- Opioids are not indicated for many forms of non-cancer chronic pain.
- Three major types of opioid receptors are involved in analgesia: mu, delta, and kappa receptors.
- Opioids are not indicated for many chronic pain conditions including headache, fibromyalgia and mechanical back pain.

Effects of cytochrome P450 system on opioid metabolism

The 2D6 isoform of CYP metabolizes codeine, oxycodone and hydrocodone, and the 3A4 isoform of the CYP system metabolizes fentanyl and methadone. Some patients have alternate forms of P450 enzymes which result in faster metabolism, usually reducing the effectiveness and duration of specific opioids. Other patients have underactive isoenzymes which may result in opioid accumulation, toxicity and even death.

Many drugs interact with 3A4 isoenzymes, and affect metabolism of methadone and fentanyl. Macrolide antibiotics inhibit 3A4 and decrease clearance of methadone and fentanyl, and phenytoin (and other antiepileptic drugs) activate 3A4 and increase methadone and fentanyl clearance.

Conclusions

Care of the patient with chronic pain is complex, requiring a multi-modal approach. Opioids play a role in the multi-modal therapy of chronic cancer pain, but on their own they very rarely alleviate pain long term. They are not indicated for most chronic non-cancer pain, and should only be used when other approaches including non-pharmacological approaches have failed. Monitoring and regular assessment is essential with referral to pain specialists in difficult cases. Most chronic pain is biopsychosocial, influenced by genetic and environmental factors, and often accompanied by physical deconditioning, anxiety, depression, insomnia and fatigue.

It is crucial to support patients and assist them with lifestyle modifications that include regular physical exercise, social interaction, and nutritious diet, and to treat insomnia and educate on sleep hygiene. These non-pharmacological modalities may be as important as taking daily medications. **BJHM**

Conflict of interest: none.

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