Opioids in the management of persistent non-cancer pain

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Abstract

One in five Europeans suffers from persistent pain which, for the majority, is non-oncological in origin. Patients with persistent non-cancer pain (PNCP) are a heterogeneous group in whom there is significant biological, psychological and societal comorbidity. Recently, there has been a large increase in opioid prescribing for PNCP, despite its limited evidence base and adverse side effect profile, including opioid dependence. This review examines the effectiveness and safety of long-term opioids in PNCP, as well as current best practice guidelines on the initiation, monitoring and titration of opioids in the out-patient setting.

Keywords Adverse effects; chronic non-cancer pain; dependence; equivalent doses; long-term effectiveness; tolerance

Royal College of Anaesthetists CPD Matrix: 2E03

Learning objectives

After reading this article, you should be able to:

- describe the role of opioids in the management PNCP
- predict adverse effects with long-term use
- explain best practice when initiating opioids in PNCP
- select equivalent doses of opioid to avoid exceeding total of 120 mg morphine per day

Persistent non-cancer pain

Persistent (chronic) pain is defined by the International Association for the Study of Pain (IASP) as pain that persists or recurs for longer than 3 months.[1] The most recent international classification of diseases (ICD-11) distinguishes between primary persistent pain (pain not better accounted for by another persistent pain diagnosis) and secondary persistent pain, which includes cancer pain and five other categories of non-cancer pain.[2]

European studies suggest that up to 20% of adults experience persistent pain, of which persistent non-cancer pain (PNCP) accounts for the vast majority.[3] PNCP has a significant impact on an individual's daily activities, employment opportunities and mental wellbeing.

Opioids have a role in the management of pain in acute, oncological and end-of-life settings but their utility in treating PNCP, where treatment goals differ, is less clear. The focus of treatment for PNCP is different — as it is aimed at improving physical and mental wellbeing, in combination with the judicious use of appropriate medication.

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Evidence for the efficacy of the use of opioids in PNCP

A recent meta-analysis of 96 randomized controlled trials (RCTs), which included 26,169 patients with various aetiologies of PNCP, found that when compared to placebo, opioids lead to a small but statistically significant reduction in pain scores. The reduction was −0.69 cm on a 10 cm visual analogue scale, and was below the 1 cm threshold that was deemed to be clinically significant at the outset of the analysis.[4] A smaller meta-analysis of 41 trials, found a small difference in pain and functional scores in favour for opioids against placebo.[5] A Cochrane review, comparing opioids against placebo for the treatment of neuropathic pain, was inconclusive.[6]

One of the main criticisms of the evidence relates to an imputational technique known as 'last observation carried forward' (LOCF). This is when a pain score of a patient who has withdrawn from the trial is included in the final analysis as if they had continued taking the drug till the end of the trial. This, coupled with a high attrition rate, presents a significant element of bias in these studies. Another drawback to the applicability of these trials is their short duration. In the two meta-analyses mentioned earlier[4,5] the median follow up was 5 weeks. A Cochrane meta-analysis focusing on longer term trials (>26 weeks) found reductions in pain scores; however findings regarding quality of life and functional status were inconclusive.[7] Convincing evidence, therefore, remains insufficient to determine the effectiveness of long-term opioid use in providing sustained pain relief and improved function for PNCP.

Adverse effects from long-term opioid use

Up to 78% of patients on long-term opiates experience adverse side effects.[8] These can include: constipation, dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus, and vomiting. Although these symptoms may subside, constipation and urticaria can persist[9] and have led to the development of mixed preparations such as oxycodone/naloxone which are aimed at improving patient compliance.

In accordance with the requirements of informed consent, patients should be counselled about these side effects prior to initiating opioid therapy. Anti-emetics and laxatives should be provided with the initial prescription as well as encouragement of adequate hydration and a high fibre diet to minimize constipation.

Respiratory depression

Sudden unintended increases in dose, and/or the addition of other sedative agents in combination with underlying risk factors

for obstructive sleep apnoea (OSA) predispose patients to respiratory depression. If opioids are to be prescribed for patients with OSA, assessments of nocturnal respiratory function as well as compliance with positive airway pressure devices should first be made.[9]

Endocrine dysfunction

Opioid receptors present in the hypothalamus can be activated by exogenous opioids. This leads to disruption of the usual pulsatile release of gonadotrophin releasing hormone (GnRH) leading to hypogonadism.

Patients may complain of reduced libido and infertility, as well as erectile dysfunction in men and menstrual abnormalities in women. A small observational study demonstrated that 85% of patients receiving intra-thecal opioids for PNCP had a biochemical diagnosis of hypogonadism and reduced bone mineral density on dual-energy X-ray absorptiometry (DEXA) scanning.[10] Patients should be referred for hormonal investigations should they present with such symptoms although, at present, guidelines state that there is insufficient evidence to recommend routine monitoring of hormone levels in asymptomatic patients.[9]

Opioid-induced hyperalgesia

Patients on long-term opioids can develop a paradoxical increase in pain symptoms known as opioid-induced hyperalgesia (OIH). Pain associated with OIH tends to differ in site, nature and severity to the original pain symptoms. Management of OIH requires a reduction in opioid dose.

Opioid tolerance, dependence and withdrawal

Tolerance has the predictable pattern over time of reducing the clinical effect of a drug. This applies to both the analgesic component as well as to the side effects of opioids. Increasing doses can overcome tolerance, but it will also increase the severity of undesirable side effects.

Opioid dependence is the persistent urge to use opioids despite harm or negative consequences arising from repeated and prolonged use of opioids. Current estimates suggest that 8–12% of patients who are currently receiving long-term opioid prescriptions meet a diagnosis for current or past opioid misuse.[9] Patients with underlying psychological distress, psychiatric illness, a history of previous alcohol or drug dependence, are at particularly high risk of developing opioid dependence.

In contrast, physical tolerance and subsequent withdrawal symptoms are almost universal among patients on long-term opioids. Symptoms can include dysphoric mood, craving, anxiety, nausea or vomiting, abdominal cramps, muscle aches, yawning, perspiration, hot and cold flushes, lacrimation, rhinorrhoea, hypersomnia or insomnia, diarrhoea and piloerection.

Guidelines for the use of opioids in PNCP

In 2015, Public Health England, in conjunction with stakeholders such as the British Pain Society, published 'Opioids Aware' – a prescribing resource to support clinicians with opioid prescribing.[9] Some of the key points from the guideline are highlighted here.

Assessment

A full pain history must include not only the characteristics of the pain, but also its impact on quality of life – such as effects on mood, sleep, physical function and previous pain experiences. Exploration of any underlying psychiatric disorder, substance misuse behaviours and social circumstances is vital.

Initiation

Opioids should only be initiated after a full trial of alternative pain management strategies and non-opioid medications. The decision to start opioids should be carefully considered and made collaboratively between the prescriber and patient.

Patient expectations need to be outlined from the start and with agreed specific functional goals. A reduction of 30% in pain is required to justify on going treatment. The aim is to reduce pain sufficiently for them to engage with self-management. An opioid initiation checklist is available for clinicians from the 'Opioids Aware' website.

Opioid trial

There is no evidence to suggest superiority of one opiate over another in terms of effectiveness or side effect profile. The choice of opioid depends on clinical judgement, local formularies and individual preference.

This being said, oral morphine should be first choice. Formulations with a rapid onset – such as intravenous, sublingual or trans-mucosal preparations – should not be used in PNCP.

The guideline suggests that to assess effectiveness, an initial opioid trial should involve prescription of an immediate release opioid formulation for 1–2 weeks. However, prolonged use of immediate release preparations is not recommended. Modified release preparations are more suitable for patients with persistent pain throughout the day and night.

Review and tapering

Patients should be reviewed within 4 weeks of commencing opioid therapy. Effectiveness, frequency of side effects and an assessment of problematic use should be made. If efficacious, opioid use may be continued and reviewed at 6 monthly intervals.

An opioid should be tapered and stopped if ineffective or with the development of significant side effects. Evidence suggests that there is a substantial increase in the risk of harm at 120 mg oral morphine equivalent (OME) per day.[9] Therefore, exceeding this dose should be avoided. Calculation of approximate equivalent analgesic potency is essential when prescribing more than one opioid formulation (Table 1).

Stopping opioids requires careful explanation of the rationale to the patient. The dose of drug can be tapered by 10% every 1–2 weeks. Patients on >300 mg OME per day may require specialist services to aid tapering.

Safety and driving

Deaths related to opioid misuse and poisoning have plateaued since 2015, despite opioid prescribing continuing to increase. The extent to which the two factors are related is difficult to establish, given how the data is collected.

Under the Road Traffic Act 1988, it is a criminal offence to be in control of a vehicle if a person's ability to drive is being

Equivalent doses for different opioids[9]

Oral opioid preparations	Equivalent dose to 10mg oral morphine
Codeine phosphate	100mg
Dihydrocodeine	100mg
Hydromorphone	1.3mg
Morphine	10mg
Oxycodone	5mg
Tapentadol	25mg
Tramodol	67mg

Transdermal opioid preparations (microgram/hr)	Equivalent oral morphine (mg/day)
Buprenorphine 5	12
Buprenorphine 10	24
Buprenorphine 20	48
Buprenorphine 35	84
Buprenorphine 52	126
Buprenorphine 70	168
Fentanyl 12	45
Fentanyl 25	90
Fentanyl 50	180
Fentanyl 75	270
Fentanyl 100	360

Table 1

impaired by drugs, whether illicit or prescribed. This ability assessment remains with the driver. Specific blood concentration limits for several drugs, including opioids, were introduced in 2015. These limits are 500 μg per litre of blood (μg/L) for methadone and 80 μg/L for morphine. This being said, patients exceeding these limits are considered not to be committing an offence provided that the prescription drugs have been taken according to the health professional's directions and that their driving ability was not impaired. Driving advice should be discussed and recorded in the medical notes at the initiation of treatment and if at any point doses are changed. ◆

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