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Opioid use in chronic non-cancer pain

Part 1: Known knowns and known unknowns

Background

Opioids have a critical, time-limited role in our management of acute and terminal pain and an open-ended role in our management of opioid dependency. They also have a use in the management of chronic non-cancer pain.

Objective

To provide an understanding of what is known, and what is not known, about the use of opioids in chronic non-cancer pain using an evidence-based approach.

Discussion

For chronic non-cancer pain, the evidence base for the long-term use of opiates is mediocre, with weak support for minimal improvements in pain measures and little or no evidence for functional restoration. Much research and professional education in this field has been underwritten by commercial interests. Escalating the prescribing of opioids has been repeatedly linked to a myriad of individual and public harms, including overdose deaths. Many patients on long-term opioids may never be able to taper off them, despite their associated toxicities and lack of efficacy. Prescribers need familiarity with good opioid care practices for evidence-based indications. Outside these areas, in chronic non-cancer pain, the general practitioner needs to use time and diligence to implement risk mitigation strategies. However, if a GP believes chronic non-cancer pain management requires opioids, prescribing must be both selective and cautious to allow patients to maintain, or regain, control of their pain management.

Keywords

opioids; chronic pain

CPD

Since antiquity, opium has played an important part in society and culture, weaving between medicine and commerce, pleasure and pain (*Figure 1* and *2*).[1] The 1960s Hospice Movement in the West fought oppressive regulations to make opioids accessible for symptomatic management of cancer pain following completion of active disease treatment.[2] Palliative care grew to take responsibility for symptom management in illnesses that were not immediately fatal but still required disease modifying treatment, such as HIV.[2] In the 1990s, palliative care specialists extended their guidelines to the general practice management of all chronic pain.[2,3] This was done without research, evaluation or meaningful input from general practitioners.[3] This shift has seen massive prescribing increases with the total number of Pharmaceutical Benefits Scheme opioid prescriptions increasing about 300% between 1992 and 2007.[4] Most opioids are being prescribed by GPs with only a minority being for cancer pain or for new problems (3.5% and 14.3% respectively).[5–7] This article reviews some of the controversies concerning the opioid management of chronic non-cancer pain (CNCP).

Indications and definitions

The main indications for prescribing opioids are for the management of opioid dependency, acute pain, terminal pain and for CNCP.

Opioid dependency has been treated with long term opioid substitutes for half a century. The risk mitigation strategies of opioid substitution therapy have found backing in over 30 randomised controlled trials (RCTs).[8]

Acute pain is a major perioperative focus of anaesthetists, but up to 41% of postoperative patients experience significant pain.[9] Moves to preference regional anaesthesia and multimodal analgesia rather than unimodal opioids aspire to improved pain relief with reduced opioid side effects.[9] These side effects include nausea, respiratory depression, acute tolerance and opioid induced hyperalgesia.[9] (Hyperalgesia being defined as an increased response to a stimulus which is normally painful.) Controversies as to the precise ending of the anaesthetist's responsibility

Figure 1. Mid-nineteenth century marketing saw the synthesis of opioids such as morphine, which was sold as a therapy for teething children

Figure 2. Diacetylmorphine ('heroin') was marketed as an over-the-counter 'non-addictive morphine substitute' for cough suppression from 1898 to 1913 and remains a prescription medicine today in the United Kingdom.

Cannabis, cocaine, nicotine and barbiturates have all variously been marketed as analgesics[1]

for analgesia[9] resemble the dilemmas faced by the GP, as acute pain becomes acute-on-chronic pain. A 10 year prospective study of acute back pain revealed a course of unpredictable recurrence in which recovery was often a temporary state, making it acute-on-chronic pain.[10]

Cancer pain used to be rapidly terminal, but this time-limiting boundary has blurred. Since 1982 in Australia, cancer 5 year survival rates have increased from 47% to 66%.[11] In the oncology community, opioids have been the cornerstone of management utilising a self titration model (liberal access, a months supply per prescription, minimal monitoring, take as much as you need).[12,13] The prevalence of abuse or addiction among cancer patients is unclear,[13] with 1980s surveys reporting rates of 0–4%.[14] However, in a cancer centre among a subgroup subject to urinary drug screening, the prevalence rate was 44.2%.[14,15] Hitherto, oncologists have regarded as foreign the risk mitigation strategies derived from opioid substitution therapy and more recently CNCP.[12,15] However, both acute and cancer pain services increasingly encounter problems such as hoarding, diversion (defined as any transfer via giving, borrowing, selling or theft), misuse (defined as use other than as directed, whether intentional or not) and addiction.[12,13]

Chronic non-cancer pain is usually defined as pain persistent beyond 3 months, deemed the duration of tissue healing.[16,17] Chronic non-cancer pain may be time-unlimited, although an annual recovery rate of 9.4% was reported in a Danish study.[2,18] Rather than treating the original acute cause, which may no longer exist, therapy serves to suppress the perceived pain.[17] The manner in which sensory stimuli become transformed into perception is complex and highly variable and involve genetic, environmental, cognitive and emotional processes.[19]

Chronic pain among Australian adults has a prevalence of almost 20%.[16,20] This prevalence is rising and the reason for this may be either apparent, from improved recording, or else real, from improved survival post-major trauma, cancer or heroic life-preserving treatments.[2,21] Pain's increasing prevalence is often equated to its undertreatment.[2,21] In 2010, the National Pain Summit agued that over 90% of Australians with chronic pain suffer undertreatment of pain making this 'the developed world's largest "undiscovered" health priority'. Most pain management advocacy has been funded by opioid manufacturers and, pharmacologically, tends to focus on improving access to opioids.[1,20–22]

Evidence about net benefits

The goals of CNCP treatment have been described as improved pain scores, function and quality of life.[23,24]

The watershed study supporting opioids for CNCP was a retrospective 1986 study of 38 patients treated in a cancer centre. Pain relief was reported by 24 and only two, both with a history of drug abuse, gave management problems.[25] Another oft cited follow up study tracked 233 selected patients on oxycodone for CNCP up to 3 years (mean duration of treatment 541 days).[26] The trial was sponsored by Purdue Pharmaceuticals and investigators were required to inform the sponsor whenever a patient showed drug seeking behaviours. Mean average pain intensity score out of 10 declined from 5.1 at commencement to 4.4 at 3 months. Average pain intensity worsened by three or more points in only 44%, permitting the conclusion that long term opioid therapy (LtOT) may provide sustained pain relief. The sponsor peremptorily terminated the study for 'administrative reasons' with only 39 patients completing 3 years.

A United States multidisciplinary expert panel identified 37 key questions requiring an answer to generate an evidence basis for the development of prescribing guidelines. A systematic evidence review was commissioned.[27] For virtually every key question, the findings identified important research gaps with critical weaknesses in the evidence.

A Cochrane review in 2009 of non-tramadol opioids in osteoarthritis identified 10 RCTs eligible for inclusion.[28] All trials claimed to be double-blind, but only three showed adequate randomisation and concealment. No study reported non-commercial funding sources. Median treatment duration was 4 weeks. Opioids gave better pain relief than placebo (2.7 cm vs 1.8 cm respectively on a 10 cm visual analogue scale). Function improved more than

placebo (1.9 units vs 1.2 units on a scale of 1 to 10). Side effects of opioids against placebo were more commonly enough to withdraw from the study (69 vs 17 per 1000 patient years: relative risk 4.05) and more commonly of a serious nature (13 vs 4 per 1000 patient years: relative risk 3.35). The Cochrane review concluded that the small to moderate beneficial effects were outweighed by large increases in the risk of adverse events.[28]

A 2010 Cochrane review found 26 studies of LtOT in CNCP eligible for inclusion that involved 4768 participants.[29] With few exceptions, they were open label case series, had commercial sponsors and excluded past substance abusers. The review found all studies were of low internal validity. For those able to remain on LtOT there was weak evidence that pain scores were lowered, although the effect on quality of life was inconclusive. Overall, the evidence for LtOT effectiveness was considered too sparse to draw firm conclusions.[29]

A 2011 Cochrane review of opioid use in rheumatoid arthritis included 11 RCTs.[30] None were considered at low risk of bias or lasted more than 6 weeks. A net benefit to harm calculation found no difference between opioids and placebo.

The most commonly prescribed pharmaceutical in the US is an opioid.[31] Yet compared to other medications, the evidence base for the effectiveness of LtOT is negligible.[22] A review noted there were about 1.8 million person years of observation in trials of medications for hypertension, three-quarters of a million person years for lipid lowering medications, but only 1500 person years in randomised trials of opioids for CNCP.[22]

Any evidence about efficacy from short term observational trials has not generalised to long term opioid use in less carefully selected and managed patient populations.[3] A Danish population wide epidemiologic study interviewed 1906 individuals with CNCP.[23] Those using opioids did not seem to be achieving the usual goals of pain management. Opioid use was significantly associated with: the reporting of severe pain, poor self rated health, inactivity during leisure, unemployment, higher healthcare utilisation, living alone and lower quality of life. In a prospective study of US workers with compensable back injuries, use of LtOT was associated with improved pain or function in only 27% and 16% respectively.[32] A Danish population study found the odds of recovery from chronic pain was decreased fourfold in individuals using opioids.[18]

The cessation of LtOT may actually improve outcomes. In 704 consecutive admissions to a US interdisciplinary chronic pain treatment program, all entrants on LtOT were tapered off. At admission those on LtOT had worse affect, sleep and mobility than non-opioid users. Both groups improved pain and function but those admitted on LtOT had similar or higher improvements.[33]

Overall, there does seem to be weak evidence of a short term improvement in pain levels with the use of opioids for CNCP in observational studies with no conclusive improvement in function or quality of life.[3] The studies had several risks for bias with one review noting 78% of the efficacy trials had pharmaceutical funding.[34] Conversely, in population studies, LtOT seems to be associated with worsening of outcomes, in terms of pain, function and recovery.

Evidence about adverse effects

Long term opioid therapy may cause adverse effects on the respiratory, gastrointestinal, musculoskeletal, cardiovascular, immune, endocrine and central nervous systems.[27,35] However, the evidence base on harms is limited being based on efficacy trials which have lacked the statistical power to detect uncommon problems or the duration to detect long term problems.[19,27] This precluded some meta-analyses from determining their incidence or significance.[19,27,29] However, a systematic review about older CNCP patients on LtOT reported constipation occurred with a median frequency of 30%, nausea 28%, dizziness 22% and somnolence 21%.[34] Long term opioid therapy is also associated with 1.4 increased relative risk of fractures in the elderly[35] and increased mortality;[18] in one review 87%.[35] Long term opioid therapy is related in a dose responsive pattern to sleep apnoeas (up to 75% vs 3–20% general population).[35,36] This may contribute to the high proportion of LtOT decedents being found in their beds.[36]

Overall, we have some evidence about the rates of the more common side effects of LtOT and emerging concerns about the adverse effects that are serious but uncommon or that are slow to develop. A useful guide for patients may be found in Baldini et al[35] (www.ncbi.nlm.nih.gov/pmc/articles/PMC3466038/table/tbl1).

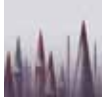
Evidence about discontinuation of opioids

Discontinuation rates are frequently higher in observational trials than in population studies, perhaps due to those ceasing treatment early not being picked up in population studies.[24] In a Swedish study 3 years after the commencement of opioids, only 51% of cancer and 27% of non-cancer patients continued LtOT.[17] However, as in many observational studies, it was unclear whether this was due to improvement in underlying condition, lack of benefit or adverse effects.

However, once established, LtOT is infrequently tapered or terminated.[24] A US healthcare data study of those prescribed opioids continuously over 90 days and then followed up for up to half a decade, showed about two-thirds remained on them.[37] It is emerging that patients who stay on opioids seem to be a self selected group who may be treating their existential suffering rather than more physically determined pain.[21,24,38] They include subgroups:

- with prior intermittent opioid prescriptions[37]
- initially risk stratified as possible misusers[37]
- with higher current rates of indicators of abuse[17,21,39]
- with higher rates of mental health and substance use disorders[17,38,40]
- who are on higher dosages or tend to dose escalate[21,37]
- who attend multiple prescribers and pharmacies.

Guidelines recommend the use of risk stratification whenever initiating LtOT, however there is often a gap between evidence and practice.[5,38] A recent New South Wales LtOT prescribing survey of 404 GPs found preliminary risk assessments were conducted with a mean reported frequency of 47%.[41] In a phenomenon described as 'adverse selection', those patients at higher risk for poor outcomes are more likely to be



initiated onto LtOT, be prescribed higher dose LtOT and avoid risk mitigation strategies.[38]

Many may never be able to come off LtOT, particularly those on higher doses.[3,37,42] They may not manifest any aberrant behaviours because they are effectively receiving opioid substitution therapy, suppressing their cravings.[42] If a clinical decision to taper the LtOT becomes necessary on risk management grounds then extreme pain, anhedonia, cravings or aberrant behaviours could emerge.[42] Some patients, unable or unwilling to taper, may need ongoing care titrated toward the structuring of a dependency program.[42]

Evidence about harms

Many of the harms from LtOT involve hoarding, diversion, abuse, overdoses and addiction.[19,39]

Hoarding was reported by over half the outpatients in a US pain clinic survey[40] and up to 42% in studies among elderly Australians.[43] Diversion is frequently quite careless and casual.[43] In a US survey of pharmaceutical opioid misusers, most sourced their drugs, not from dealers, but from friends or family.[44] These opioids were given freely (56%), purchased (9%) or stolen (5%). The friend or family member who diverted them usually (82%) had obtained them from just one doctor.[44] Of 352 US pain clinic patients, 45% experienced diversion of their LtOT at least once, most commonly loss through theft.[45] Similarly in Australia, borrowing or sharing medications is commonplace especially among certain ethnic groups.[43]

The past year prevalence rate of pharmaceutical opioid abuse in Australia is estimated to be 3.0%.[46] Opioid related deaths, which dropped after the heroin drought of 2001, have recommenced, returning to pre-drought levels among older Australians.[47] Overdoses occurred at a high rate (1.8% per annum) among those prescribed at least 100 mg morphine equivalents in one US study,[48] although the majority of overdoses occurred in the larger groups of people receiving lower doses. For every unintentional pharmaceutical opioid overdose death, US figures estimate nine are admitted for addiction treatment, 35 visit hospital emergency departments, 161 report drug abuse or dependence, and 461 report non-medical uses of opioid analgesics.[49] This latter is easily missed despite its frequency. Of 26 314 Americans on opioids in one study, a minority (19%) used the medication as prescribed, self medication was reported in 43% (significantly associated with psychoemotional issues), 27% used recreationally and 18% used chaotically, as seen with heroin dependency.[39]

The predominant opioids of misuse in Australia, New Zealand and North America, have now become the pharmaceuticals.[31,50]

Conclusion

The prescribing of opioids has escalated despite the evidence that the benefits of LtOT have been overstated and the individual and public health harms have been understated.[19,22,27] However, if a GP believes CNCP management requires opioids, prescribing must be both selective and cautious[3] to allow our patients to maintain, or regain, control of their pain management.

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