



Opioids for chronic noncancer pain

The use of strong opioids as analgesics is established practice when managing postoperative pain and that associated with a terminal illness. It is now becoming more accepted in the treatment of chronic noncancer pain. This use is supported by significant evidence of an analgesic effect. However, a number of issues including efficacy in comparison with other drug classes and the risk of obvious and more insidious short- and long-term side effects, cause a degree of concern that may mitigate against even more widespread use.

KEYWORDS: fentanyl ■ morphine ■ neuropathic pain ■ opioids ■ oxycodone ■ pain

The number of available opioid preparations, each with differing chemical properties, structure and opioid receptor affinity, increases with time. The efficacy of these opioids in the treatment of pain arising from a diverse range of disorders is beyond question. With the passage of time, the list of those conditions where an opioid is recommended as a treatment option increases, and that list now includes those that generate chronic pain both of a nociceptive and neuropathic type [1]. With relatively few licensed/approved options for the analgesic management of chronic pain disorders, the availability of strong opioid formulations with such indications increases the likelihood of the practitioner selecting this type of drug as their preferred management choice. To confuse matters, licensing and approvals for drugs differ from one country to another. However, the presence of an approved indication for the use of a strong opioid in the treatment of a specific chronic pain condition does not mean that they are necessarily the best choice in that patient's treatment plan.

Has opioid treatment a place in the management of chronic pain? The answer is without doubt 'yes'. Many, indeed most, patients will have taken an opioid early on in their treatment in the form of codeine or other weak opioid. Whether that treatment is effective, or indeed evidence based, is less certain, but the wide diversity of codeine-containing preparations available suggests that patients and their general practitioners see merit in the use of opioids. Clearly, the pharmaceutical industry also sees these type of drugs as an important option from a commercial perspective.

The issue, therefore, is whether the use of strong opioids (opioids for severe pain) has a place in the treatment of chronic pain. The

answer to this question could be perceived as either 'yes' or 'no'. In reality, as we will see, the wisest response may actually be 'sometimes, but not always'.

The argument falls into two sections. First, why they should be considered for the treatment of chronic pain, and second, why they should not be selected. With a fusion of this knowledge the practitioner can make a balanced judgement on the wisdom of this line of treatment.

Reasons why strong opioids should be chosen for the management of chronic pain

The fundamental reason is because they work, or perhaps more accurately that there is a strong body of evidence showing that they have a greater pain-relieving effect than placebo when these are compared.

Eisenberg and colleagues have published a systematic review and meta-analysis of trials evaluating the safety and efficacy of opioids in the treatment of neuropathic pain of non-malignant origin. Of the studies they examined, 14 measured pain over the short term (<24 h), while eight of the analyzed studies measured pain over a range of 8–56 days. The short-term trials had contradictory results. However, all studies of longer duration demonstrated that opioids were effective for neuropathic pain [2].

In a report of the efficacy and safety of strong opioids in the treatment of severe noncancer pain, Kalso and colleagues analyzed data from 1145 patients initially randomized in 15 placebo controlled trials. Four studies tested intravenous opioids in neuropathic pain in a crossover design, with 115 of 120 patients initially enrolled

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completing the protocols. Using pain-intensity difference or pain relief as the end point, all four intravenous studies reported average pain relief of 30–60% with opioid [3].

Eleven of the studies Kalso and colleagues examined (1025 patients) compared oral opioids with placebo for 4 days to 8 weeks. Six of the 11 studies had an open-label follow-up of 6–24 months. The mean decrease in pain intensity in most studies was at least 30% with opioids, and was comparable in neuropathic and musculoskeletal pain. Approximately 80% of patients noted at least one adverse effect, with constipation being the most frequently noted (41% of subjects). Nausea was noted in 32%, and somnolence in 29%. Only 44% of 388 patients on open-label treatments were still on opioids after therapy for between 7 and 24 months. Adverse effects and lack of efficacy were two common reasons for opioid discontinuation [3].

Furlan and colleagues looked at 41 studies, comprising a total of 6019 patients taking opioids for noncancer pain, and concluded that opioids outperform placebo for all types of noncancer pain [4]. Chou *et al.* analyzed 22 studies and concluded that opioids are effective for neuropathic pain, but that side effects were common [5]. Although evidence is limited, an expert panel concluded in 2009 that chronic opioid therapy can be an effective therapy for carefully selected and monitored patients with chronic noncancer pain [6].

Factors militating against the use of strong opioids in chronic noncancer pain

We have seen that a body of evidence supports the use of strong opioids in patients with a variety of pain-producing conditions. But are they the best option for that patient? An obvious statement regarding treatment provision is that a patient should receive drug treatment that is the most simple possible – that is, that it is effective and exposes the patient to the lowest risk of both short-term and long-term adverse events, and often insidious side effects arising from that treatment. Prescription of medication should be on the basis of a risk:benefit analysis for each step on the suggested treatment algorithm for that patient. What confounds this approach is that on some occasions treatment options have obvious superiority over others, but do not have an approved indication for treatment in that condition, and so the practitioner may be put off selecting that option for their patient. As things stand, we still lack comparative data that would

allow comparison of other treatments with that of strong opioids (opioids for severe pain). While such comparative data would be of greatest interest to clinicians, the difficulties in performing such studies in a meaningful way put most investigators off carrying out such work.

While strong opioids (opioids for severe pain) have been used in pain treatment in one form or another through the generations, we still do not have a proper understanding of the long-term consequences of strong opioid treatment. For example, do strong opioids always retain their initial analgesic potential, even after years of use? The issue of analgesic tolerance – that is, a need to increase dose to achieve the same initial analgesic effect – remains controversial and unresolved, with some contending that analgesic tolerance does not complicate strong opioid use in humans, with others being more sceptical. What is beyond argument is that antinociceptive tolerance is easy to reproduce in animal pain models. Of equal clinical significance is the problem of withdrawal reactions from opioid use. These can be severe and most unpleasant, and have a major impact on the patient's quality of life. Therefore, thought should be given to this complication before opioid therapy is commenced. Withdrawal of opioid can be intentional when a decision is made to discontinue, or even just reduce dose because of overall improvement in the patient's condition, lack of efficacy or availability of an alternative. Withdrawal can also be unintentional when the patient runs out of supply or does not absorb the drug, as when an oral strong opioid is used in a patient with acute nausea and vomiting from whatever cause. While the practitioner may make a judgement that a strong opioid is the best treatment available for management of an individual's pain, and is happy to escalate the dose as need arises, what then happens in the future if some much superior alternative treatment becomes available? Is the strong opioid (needlessly) continued so as a withdrawal reaction is avoided, or is the patient forced to undergo such a withdrawal reaction in order to discontinue opioid therapy? Would the patient be happy to have therapy with an opioid initiated if they were fully conversant with the nature and severity of opioid withdrawal reactions?

On initiation of strong opioid therapy, effects on cognition may be observed. In a study of 124,655 patients in Denmark it was found that opioids were being taken by 8.0% of subjects who had sustained a fracture, whereas only 3.2% of 373,962 control subjects not taking opioids sustained fractures. The odds ratio for sustaining

a fracture were 1.47 with morphine, 2.23 with fentanyl, 1.39 with methadone, 1.36 with oxycodone, 1.54 with tramadol, 1.16 with codeine and 0.86 with buprenorphine [6]. That said, other reports suggest a decrease in fall frequency in patients taking strong opioids when compared with similar patients not taking these drugs [7].

Isolated reports also suggest that opioids, when given long term by the intrathecal route, cause hormonal changes, with decreased testosterone levels and impotence in males, and decreased luteinizing hormone, estradiol and progesterone, with irregular cycle or amenorrhea in females, with all having decreased urinary cortisol levels [8]. A single report of inappropriate antidiuretic hormone release with transdermal fentanyl has been published [9].

Other animal and human studies report the onset of paradoxical pain and hyperalgesia with sustained opioid use [10,11]. For example, in a human model it has been shown that the area of skin with induced mechanical hyperalgesia is significantly increased after discontinuation of a remifentanyl infusion when compared with subjects not receiving this ultra-short-acting opioid [12]. While remifentanyl is not an opioid that is used in chronic pain management, its short half-life may allow observable changes in analgesic tolerance to be measurable in a human experimental scenario and suggests, but does not prove that changes in analgesic tolerance may occur with sustained use. If such paradoxical pain occurs and remains unidentified, it may lead to an increase in opioid dose, with a potential increase in opioid-related side effects and consequent reduction in tolerability. Opioid-induced paradoxical pain may be caused by opioid-induced release of spinal dynorphin [13] and cholecystokinin [14].

In addition to these potential complications of long-term strong opioid use, initiation of therapy is often associated with nausea and even vomiting, while constipation is not infrequent in the longer term [15]. However, these are predictable and common side effects, and so initiation of strong opioid therapy can be covered by co-prescription of antiemetics in the short term and by constant attention to bowel frequency and prophylactic laxatives use for most patients. It could indeed be argued that knowledge of the likelihood of these side effects and availability of preventative treatments should not be deterrents to strong opioid prescription.

Another complicating issue surrounding the use of strong opioids concerns the patient's ability to drive motor vehicles. It seems that cognitive impairment is unlikely when a stable dose

of opioid is used and the patient is habituated to its use. However, caution should be taken when dose escalation is taking place.

One last series of factors should be borne in mind. We live in an age where substance abuse is widespread, and the unintentional act of adding a 'medicinal' opioid to one which the patient takes on a 'recreational' basis, or the adding of an opioid in a patient taking other forms of illicit drugs, may be dangerous and certainly is questionable. Therefore, a careful history needs to be taken from the patient before the use of strong opioids is contemplated. One may even go as far as to insist that the patient signs an opioid 'contract', which states that any inappropriate use of the strong opioid, or the intentional use of other illicit drugs when on the medically prescribed opioid, will lead to treatment withdrawal [16].

Outstanding issues surrounding use of strong opioids (opioids for severe pain) in patients with chronic pain

Increasing data supports the use of strong opioids in the treatment of a variety of chronic pain conditions. However, there is a paucity, indeed often an absence of data, relating to some issues regarding the use of strong opioids. For example, if a patient has a cancer-related pain, strong opioid use is common. The patient is provided with an extended-release preparation, and often an immediate release variety of the same drug to deal with breakthrough pain. However, there seems little consensus as to whether a similar approach should be taken with patients with chronic pain not related to a terminal illness. Many will feel that the availability of immediate-release strong opioids for use in a patient with chronic pain increases the likelihood of addiction, as the sudden release of the opioid causes a rapid increase in serum level of the opioid, with the consequent opioid euphoria and other psychogenic manifestations not seen when an extended-release opioid is used. It could also be argued that the rapid decline in serum opioid levels soon after drug administration could be complicated by a mini withdrawal reaction, which has amongst its manifestations an increase in pain perception, and hence a desire to retake the immediate-release opioid.

Another area that needs more elucidation relates to the analgesic efficacy of opioids. When one observes the use of strong opioids in post-operative pain management, one sees them to be effective for relieving pain at rest. When the patient goes to move, breath deeply or cough, then they are significantly less effective. Hence

the widespread use of postoperative epidural analgesia where the evidence points to earlier mobilization and a reduction in respiratory complications. Why then should we assume that strong opioids do not have the same effect when used for chronic pain? Could they not give satisfactory analgesia when the patient is at rest with suboptimal pain relief when they go to move?

It is felt by some that tolerance to the analgesic effect occurs when strong opioids are used. If this is so, then why has more attention not been given to strategies that reduce the onset of analgesic tolerance? For example, strong bodies of evidence suggest that co-administration of cholecystokinin antagonists in animal pain models prevents the onset of antinociceptive tolerance [17,18], while similar administration in animals already showing antinociceptive tolerance reverses that phenomenon [19,20]. Similarly, animal work suggests that the use of 5HT₃ antagonists prevents antinociceptive tolerance [21].

Perhaps the most pressing question for the clinician is which opioid and which mode of administration obtains the best results? Indeed, are there significant advantages at all when one strong opioid is compared with another, either in terms of analgesic efficacy or side-effect profile?

Questions that may be asked before strong opioids are initiated

In my view the following questions need to be answered before strong opioid therapy is initiated:

- Is a strong opioid the best form of treatment available for the presenting pain?
- Will the opioid interact in a negative fashion with any concomitantly administered 'medicinal' or illicit drugs?
- Can other therapeutic agents be added to minimize the dose of opioid required to achieve analgesia?
- Can other agents be added to minimize the risk of analgesic tolerance?
- Which route of administration is most appropriate?
- Which strong opioid should be chosen?
- At what dose will the opioid be initiated?
- What is the expected duration of treatment?
- Will rules be imposed that limit the rate of dose escalation?

- Will there be a limit to the dose of opioid used?
- How will the effect of treatment be measured?
- After what period of time will the effect of treatment be assessed?
- Will the therapy be kept under long-term review?

Conclusion

Strong opioid therapy has a well-deserved place in the treatment armamentarium of those treating chronic pain. There is evidence of analgesic efficacy and this evidence is growing. However, the issues surrounding opioid therapy, such as comparative efficacy when compared with other pain-relieving drugs and the safety of their use in the short- and long-term demand that the prescriber makes a balanced judgement regarding the wisdom of their use. We have (thankfully) passed through an age where 'opioid phobia' was prevalent, but it seems to this author that perhaps the pendulum has swung too far in the other direction, and that strong opioids are seemingly prescribed with an abandon that shows little thought for the best interest of the patient. Prescribe, yes, but only after careful thought.

Future perspective

How will the use of strong opioids in the management of noncancer change over the next 5–10 years? It would be my opinion that we will not have significantly improved the quality of our strong opioid prescriptions over this timescale. We will still lack comparative data that compares the effect of individual strong opioids with one another, as well as the differences in effect between strong opioids and other classes of analgesic medication. There will also be more strong opioid preparations in differing formulations that will further confuse the situation. Furthermore, with the increased tendency for nonspecialist prescription of strong opioids, the quality of decision-making regarding their use may lessen.

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Executive summary

- The use of strong opioids by medical practitioners is increasingly being accepted for the treatment of chronic noncancer pain.
- The licensed indications for strong opioids varies from country to country.
- Strong opioids can be effective for the treatment of chronic noncancer pain, but are not universally so.
- Strong opioids are an important treatment to be considered for the treatment of chronic noncancer pain, but there are often other therapeutic options whose use should also be contemplated.
- We lack comparative data comparing the effects of strong opioids with other treatment options.
- The issues of analgesic tolerance and its prevention with strong opioid use remains to be resolved.
- The consequences of long-term strong opioid use, such as endocrine changes and paradoxical pain, remain to be properly defined.

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