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Supplement

Conventional and atypical opioids

Not all opioids are the same

The atypical opioids: buprenorphine, tramadol and tapentadol

Use of opioids in chronic noncancer pain

Acute and chronic musculoskeletal pain – pharmacological management

Tapering off opioid analgesia

Opioid prescribing in general practice: a proposed approach

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CONVENTIONAL AND ATYPICAL OPIOIDS
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FOREWORD FROM THE SUPPLEMENT EDITOR

Over the past 30 years, opioids have been on a rollercoaster ride. This ride began with the 'opiophobia' of the '80s, which was then successfully overcome, at least in developed countries, by the UK's hospice movement and the WHO through its step-ladder approach to cancer pain. Subsequently, the success of opioids in the management of cancer pain was inappropriately translated to all chronic noncancer pain, ignoring the complexity of the sociopsychobiomedical origin of most of these pain states.

The new approach did not help most sufferers of chronic pain to achieve their goals of improved quality of life and reduced disability, but resulted in increased risks of opioid abuse and even fatal overdose. Shocking mortality statistics and headlines such as 'A flood of opioids, a tide of rising deaths' (in *The New England Journal of Medicine*) led to the recognition of the 'opioid epidemic' as a major healthcare issue.

It is therefore necessary to stress the relevance of a multimodal and interdisciplinary approach to the management of chronic pain with an emphasis on active treatment strategies leading to self-efficacy and self-management. Medications can sometimes help to achieve these goals, but with regard to opioids this should be preferably with use of atypical opioids. The atypical opioids, transdermal buprenorphine, tramadol and tapentadol, have different mechanisms of action than conventional opioids that rely exclusively on mu-receptor agonism. This explains their different effects and adverse effects, as well as their lower risk of abuse and toxicity.

This supplement addresses concepts of chronic pain management and important principles of the use of opioids in this setting.

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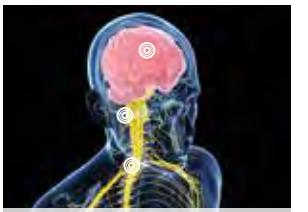

PAGE 5

FEATURE ARTICLES PEER REVIEWED

PAGE 12

PAGE 16

PAGE 26

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Not all opioids are the same

STEPHAN A. SCHUG MD, FANZCA, FFPMANZCA, EDPM

Opioids are the most effective analgesics available but when used inappropriately can cause problems to individual patients and society as a whole. Recognising the differences between conventional and atypical opioids can help prevent some of these adverse consequences.

Opioids have been used by humans for many thousands of years.[1] Initially, these were extracts of the poppy seed, which were then chemically defined in the form of morphine and subsequently modified by the pharmaceutical industry to the wide range of medicines available to us today. Opioids as we know them today differ in potency, pharmacokinetics and metabolism, but most rely primarily on their agonist activity on the mu-opioid receptor for their analgesic efficacy.

Opioids are the most effective analgesics available and are mandatory components of pain relief in the setting of severe acute pain, such as after surgery and trauma, or severe cancer pain. However, opioids are not harmless and the potentially life-threatening adverse effect of opioid-induced ventilatory impairment (OIVI) and unpleasant side effects such as nausea, vomiting, constipation, urinary retention, sedation, confusion or agitation have been well described.[1,2]

Overcoming the fear of opioid use

Initially opioids were freely available in many countries, but increasing concerns about abuse and addiction resulted in restrictive legislation such as the Harrison Narcotic Act in the US in 1914.[1] These concerns resulted in widespread 'opiophobia' among medical practitioners, other healthcare professionals and even patients.[3] This fear of creating addiction limited the use of opioids in appropriate settings such as for cancer pain, and was finally overcome by the UK's hospice movement and the WHO's recommendations for cancer pain management.[4,5] However, these changes occurred primarily in developed and industrialised countries, whereas large parts of the world population still have insufficient access to opioids for the management of acute and cancer pain.[6]

Opioids in chronic noncancer pain

In the 1990s, the success of increasing opioid use for cancer pain led to suggestions that similar benefits could also be achieved in patients with chronic noncancer pain.[7,8] This resulted in a dramatic increase in the use of opioids for this indication in several countries including Canada, the US and Australia, with significant consequences for patients and society as a whole.[9,10] However, simply transferring the concepts and findings of acute and cancer pain management to the treatment of chronic noncancer pain was regrettably a flawed concept.

In line with early concerns about this approach, managing the complexity of the sociopsychobiomedical phenomenon of chronic noncancer pain with opioids

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was not beneficial to many patients, particularly with long-term use.[11-13] As shown in a wide range of randomised controlled trials summarised in meta-analyses, long-term opioid treatment of chronic noncancer pain results only in very limited pain relief and in particular almost no improvement in function and quality of life.[14,15] These disappointing outcomes have been confirmed in many observational and epidemiological studies, which often also show a deterioration of function and quality of life with long-term opioid use.[16,17]

The phenomenon of opioid-induced hyperalgesia seems to increase central sensitisation and therefore the pain experience in many patients, particularly those taking high doses of opioids.[18,19] Further, adverse outcomes are caused by opioid-induced androgen deficiency (OPIAD) leading to hypogonadotrophic hypogonadism with very low testosterone levels and sequelae such as depression, fatigue, weight gain and decreased muscle mass, contributing to further deterioration of the quality of life of patients affected by chronic pain.[20]

Conventional mu-agonist opioids suppress immune function and this has clinical consequences with regard to increased infection risk.[21,22] The potential risk of OIVI, leading to increased mortality among opioid users, is dose-dependent and therefore increases when attempts to control pain lead to excessive dosing.[23] Last, but not least, physical dependence, misuse and abuse and the development of addiction in susceptible patients have become a serious problem in countries with high opioid prescribing for chronic noncancer pain.[24]

Effects of excessive opioid use on society

In addition to the negative consequences of inappropriate opioid use for many individuals, there have also been harmful consequences to society with increased diversion of prescription opioids into the black market and a dramatic increase in deaths associated with prescription opioid misuse and abuse.[24-26] Similar trends on a smaller scale have now also been described in European countries including France;[27] however, the findings from Canada, the US and Australia are particularly worrying.[10] Overall, the 'caring' concept of providing people experiencing chronic pain with pain relief by prescribing them opioids has proven to have 'crippling' consequences not just for the individual patients, but also for society as a whole.[28]

Not all opioids are the same

These dramatic consequences have led to an interesting discussion about whether all opioids are the same. Prominent researchers in the area of opioid pharmacology, such as the pharmacologist R. Raffa, have suggested that 'categorisation of all analgesics that have any component of opioid mechanism of action into the same class is anachronistic'.[29] This suggests a separation of conventional (or classical) opioids, with their mechanism of action primarily based on mu-opioid receptor agonism, from atypical opioids, which have multiple mechanisms of action and rely only partially on mu-receptor agonism. The substances buprenorphine, tramadol, tapentadol and cebranopadol fulfil this definition of atypical opioids.

Atypical opioids

Three atypical opioids (buprenorphine, tramadol and tapentadol) are currently marketed in many countries worldwide, while cebranopadol is undergoing phase II trials.[30] Research over the past 10 years has increasingly shown that buprenorphine, in particular as a patch for transdermal administration, as well as tramadol and tapentadol may have superior efficacy in chronic pain, in particular with regard to the desired most relevant outcomes of improved function and quality of life.[31-37] In addition, they have less serious adverse effects on immune function and the endocrine system, lower rates of some other adverse effects (such as gastrointestinal ones) and carry a reduced risk of OIVI, and thereby death, in high doses.[38-41] Finally, these atypical opioids have a lower abuse potential than conventional opioids and therefore a lower risk of misuse, abuse and diversion into black markets.[40,42]

The recognition that there is a profound difference in efficacy, adverse effects and safety between conventional opioids and atypical opioids may offer new and interesting avenues for the management of chronic pain. MT

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The atypical opioids

Buprenorphine, tramadol and tapentadol

STEPHAN A. SCHUG MD, FANZCA, FFPMANZCA, EDPM

There are many differences between conventional and atypical opioids, including different efficacies, adverse effects and toxicities, as well as risk of abuse. These factors should be considered when prescribing opioids for chronic pain conditions.

When the mechanism of action of tramadol was unravelled in the late 1990s, it became obvious that, contrary to preceding beliefs that it is a partial mu-receptor agonist, it relies on multiple mechanisms of action including weak mu-receptor agonism.[1] This recognition resulted in the early suggestion to describe tramadol as an 'atypical opioid' in contrast to the conventional (or classical) opioids. Subsequently, it became obvious that tramadol, and also buprenorphine and tapentadol, have mechanisms of action that do not exclusively rely on mu-receptor agonism.[2]

It has, therefore, been suggested that the atypical opioids buprenorphine, tramadol and tapentadol (as well as cebranopadol, which is currently under investigation[3]), be classified separately from the conventional opioids such as morphine, oxycodone, hydromorphone and fentanyl. This separation is not only scientifically useful on the basis of the different mechanisms of action, but also clinically relevant as this translates into different efficacies, adverse effects and toxicity. It is the intention of this review to summarise the current knowledge about these atypical opioids.

KEY POINTS

- Atypical opioids differ from conventional opioids as they do not rely exclusively on mu-receptor agonism for their analgesic effect.
- The atypical opioids, buprenorphine, tramadol and tapentadol, have different effects and different adverse effects including toxicity and abuse potential compared with conventional opioids.
- These differences result in improved outcomes and reduced risks with the use of atypical opioids for individual patients and society as a whole.
- Atypical opioids are the preferred strong analgesics for chronic pain that requires pharmacological treatment.
- Tapentadol in particular seems to offer the best risk-benefit ratio in the pharmacological management of chronic pain with proven efficacy in nociceptive, neuropathic and mixed pain conditions, best tolerability and good safety data.

Buprenorphine

Pharmacology

Buprenorphine has the most complex pharmacology of the three atypical opioids discussed here.[4] Our understanding has changed over time, but this has not yet been fully elucidated. These issues have resulted in some contradictory messages in the literature

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and significant confusion among clinical practitioners.[5] Briefly, buprenorphine is a potent but partial agonist at the mu-opioid receptor with high receptor affinity explaining its long duration of action.[6] It is also a potent kappa-receptor antagonist.[5] Furthermore, buprenorphine is an agonist at the nociceptin or opioid-receptor-like 1 (ORL-1) receptor; the latter effects possibly explain some of the many advantageous effects of buprenorphine.[7] In addition, buprenorphine binds to delta-opioid receptors.

Overall, buprenorphine behaves quite differently from conventional opioids with primarily mu-agonist effects. The interplay between these multiple receptor effects is complex and species-specific. For example, the inverted U-shaped dose-effect curve for buprenorphine that was found in rodents led to concerns over a possible submaximal analgesic effect in humans, but this has not been confirmed in clinical practice.[5]

Efficacy

Buprenorphine has been extensively investigated as a sublingual preparation, in particular for opioid substitution in the management of opioid addiction.[8,9] In this setting, the analgesic effects of buprenorphine are sufficient to cover severe postoperative pain, therefore leading to a reversal of the previous advice to discontinue buprenorphine substitution before major surgery.[10] Contrary to the findings in animal experiments, all available data on humans show no analgesic ceiling effect with no plateau of the dose-response curve in clinically meaningful doses and no antagonistic effect of buprenorphine when combined with other mu-agonists.[11,12]

The high potency and good lipophilicity of buprenorphine made it an ideal candidate for the development of transdermal delivery systems.[13] Most value for the treatment of cancer and chronic noncancer pain lies in use of these buprenorphine patches for transdermal application;[14,15] the following text will primarily address transdermal buprenorphine, if not otherwise stated.

In comparative trials, buprenorphine has provided equivalent analgesia to morphine, hydromorphone, oxycodone, fentanyl and methadone.[7] The conversion from transdermal buprenorphine to oral morphine suggests an equianalgesic ratio in the range of 1:110.[5,16] Buprenorphine also has proven efficacy and low rates of toxicity in elderly patients and its effects are minimally affected by renal failure or haemodialysis.[7]

Safety and adverse effects

Buprenorphine has a ceiling effect for respiratory depression, and it is likely that respiratory depression linked to buprenorphine is primarily caused by its active metabolite norbuprenorphine.[17,18] The observation of this ceiling effect reduces the risk of respiratory depression, but does not mean that buprenorphine has no respiratory depressant effect;[6] there are published reports of fatalities and significant respiratory depression with sublingual buprenorphine.[19,20] In this context it is of interest that, although combinations of buprenorphine with a benzodiazepine increase the risk of fatal outcomes,[19] they seem to be safer than methadone with a benzodiazepine.[21] With transdermal buprenorphine, respiratory depression with fatal consequences has a zero incidence in a data analysis from the US National Poison Data System.[22]

With regard to long-term use, buprenorphine seems to cause less tolerance than conventional mu-receptor agonists such as fentanyl.[23] It has an antihyperalgesic effect and may attenuate opioid-induced hyperalgesia, possibly due to less glial activation via Toll-like receptor 4, an important mechanism in central sensitisation and neuropathic pain, but also in opioid-induced hyperalgesia.[24-26]

Conventional opioids have significant immunosuppressive effects, which have been recently related to dose-dependent increases in infection risk with long-term opioid use.[27,28] In the experimental setting, buprenorphine does not reduce natural killer cell activity and seems to be less immunosuppressive;[29,30] these data have not been confirmed in humans and their clinical relevance is unclear.[6] With regard to hypogonadism and testosterone suppression (opioid-induced androgen deficiency), the effects of buprenorphine seem to be minimal compared with conventional opioids.[31]

It has been shown in several studies that buprenorphine causes less cognitive dysfunction than conventional opioids with regard to parameters such as visual pursuit test and driving-related psychomotor battery, as well as complex psychomotor and cognitive performance.[7] These experimental data may even translate into improved clinical outcomes; in an epidemiological study buprenorphine was the only strong opioid not linked to an increased fracture risk due to falls.[32] Other advantages of buprenorphine are less constipating effects, in particular when administered transdermally, where it causes less constipation than even transdermal fentanyl.[6] Specific adverse effects of transdermal buprenorphine are local skin reactions, in particular erythema and pruritus, which are more common than with transdermal fentanyl and may be reduced by topical corticosteroid administration.[33]

Dependence, abuse potential and diversion

Buprenorphine is a partial mu-receptor agonist, which results in 'drug liking' and is therefore associated with abuse potential, withdrawal and diversion in its sublingual preparations.[34] However, buprenorphine is not as well 'liked' as full mu-receptor agonists. In particular, the transdermal preparation with stable plasma concentration seems to be unattractive for drug seekers. This is confirmed by US data showing that prescription-adjusted rates of intentional abuse and suspected suicidal intent with transdermal buprenorphine were significantly lower than for morphine, oxycodone, oxymorphone, methadone and transdermal fentanyl.[22]

Physical dependence and withdrawal symptoms occur with buprenorphine, but are reported as milder than with conventional opioids, e.g. in a double-blind comparison with morphine;[35] however, to

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reduce these symptoms gradual dose reduction is recommended.[6]

Tramadol

Pharmacology

Tramadol is the prototype of the atypical opioid and the first compound to be described with this label in the literature.[1] Tramadol has analgesic effects based on three mechanisms: the mu-receptor agonist effect primarily of its main metabolite O-desmethyltramadol (M1), as well as noradrenaline reuptake inhibition and serotonin reuptake inhibition.[36] Both of the latter mechanisms strengthen descending pathways of pain control by increasing the synaptic concentration of inhibitory neurotransmitters.[37]

In animal experiments using appropriate antagonists, about 40% of the analgesic effect of tramadol was found to be based on mu-receptor agonism, about 40% on noradrenaline reuptake inhibition and about 20% on serotonin reuptake inhibition with synergism between these mechanisms.[38] However, this may be different in humans, partially because the contribution of the mu-receptor effect is mainly dependent on the active metabolite M1, which has about 200 times greater affinity for the mu-receptor than tramadol itself.[37] The O-demethylation of tramadol to M1 is catalysed by cytochrome P450 (CYP) 2D6; metabolisation is thereby dependent on the polymorphism of the gene encoding this enzyme. People who are poor metabolisers have significantly lower M1 plasma concentrations than extensive metabolisers.[39] This has been confirmed in studies showing that poor metabolisers required more tramadol to achieve the same analgesic effect and had a poorer analgesic response than extensive metabolisers.[40] There might also be an increased risk for mu-opioid receptor effects such as respiratory depression in ultra-fast metabolisers achieving high M1 plasma concentrations.[41]

Efficacy

In comparative trials with other opioids administered by patient-controlled analgesia, tramadol had comparable analgesic efficacy to conventional mu-receptor agonists such as morphine, fentanyl and oxycodone.[42] However, in clinical practice, it has limited efficacy partially due to a recommended maximum dose of 400 to 600 mg daily.

Tramadol has been successfully used in patients with cancer pain as a step-two drug on the WHO ladder, as well as in those with chronic noncancer pain, where it had also beneficial effects on physical function with reduced disability.[43-45] In osteoarthritis specifically, tramadol improved pain scores and function to some extent.[46] Tramadol is also an effective compound for the treatment of neuropathic pain with a number needed to treat of 3.8.[47] It is the only opioid listed as a second-line treatment for neuropathic pain in the guidelines from the Special Interest Group on Neuropathic Pain.[48]

Safety and adverse effects

Due to the difference in pharmacology from conventional opioids, tramadol's adverse effect profile also looks different. With regard to safety, the risk of respiratory depression is significantly lower than with the conventional opioids oxycodone and pethidine at equianalgesic doses.[49-51] Tramadol does not depress the hypoxic ventilator response.[52] However, it can cause respiratory depression, particularly with overdose, and fatalities have been reported, although the number of cases is very low.[53] In this context, it might be important to consider that the active metabolite M1 is excreted as a glucuronide via the kidney and therefore renal failure may lead to accumulation of this active metabolite.[41,54]

Tramadol lowers the seizure threshold, most likely by its serotonergic effects.[55,56] Therefore, it causes more seizures than conventional opioids, particularly with overdose.[53] This increased seizure risk was also shown in comparison with tapentadol in the US National Poison Data System.[57] However, comparative epidemiological studies have not confirmed a higher seizure rate for tramadol than those of conventional opioids in routine clinical use.[58,59]

The serotonergic effects of tramadol lead to an increased risk of serotonergic reactions, and in rare cases serotonin syndrome, when combined with medications also having a serotonergic effect such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs).[56,60] The risk is higher in people who are CYP2D6 poor metabolisers and those taking SSRIs that inhibit CYP2D6 such as sertraline, paroxetine or fluoxetine, as both scenarios lead to increased tramadol concentrations.[60,61] Another relevant drug interaction is between tramadol and 5-HT(3) receptor antagonist antiemetics, described in particular for ondansetron.[62] The interaction is most likely pharmacokinetic (via CYP2D6) and pharmacodynamic (via opposite effects on serotonin effects) leading to reduced efficacy of both drugs.[60,63,64]

The serotonergic effects of tramadol resulted in an increased rate of nausea and vomiting in several comparative trials with other conventional opioids such as morphine, fentanyl and oxycodone.[42] An increased rate of confusion and delirium in elderly patients has also been described.[65]

Tramadol causes significantly less constipation than conventional opioids primarily due to a less inhibitory effect on gastrointestinal motor function.[37] Animal data support less immunosuppressive effects of tramadol, which is not surprising in view of the low mu-receptor agonist effect of this compound.[66] Human data confirm this, but again there are no clinical outcome data in line with these findings.[67]

Dependence, abuse potential and diversion

Tramadol can cause physical dependence, but with a lower incidence and lower severity of withdrawal symptoms than conventional opioids.[68] Atypical withdrawal symptoms similar to those observed with SSRIs or SNRIs can also occur.[69] Tramadol has been used

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successfully in opioid withdrawal and was found to be superior to clonidine and comparable with buprenorphine in reducing withdrawal symptoms.[70]

Although abuse of tramadol has been reported, the abuse potential is much lower than that of conventional opioids.[37] These findings are in line with US data, which show tramadol to have a comparable rate of diversion to tapentadol and a significantly lower rate than conventional opioids.[71] This is also supported by several extensive studies, performed in particular in the US, leading to a lower scheduling of tramadol than conventional opioids in most countries;[72,73] this assessment has been confirmed by expert committees, such as in Germany.[74]

Tapentadol

Pharmacology

The analgesic effect of tapentadol is based on its combined effect as a mu-opioid receptor agonist and a noradrenaline reuptake inhibitor.[75] The affinity of tapentadol for the human mu-receptor is about 18 times lower than that of morphine (but tapentadol is only three times less potent than morphine), whereas the reuptake inhibition of noradrenaline is similar to that of an SNRI such as venlafaxine. The high analgesic efficacy is explained by the extensive synergy between the two mechanisms of action as shown in site-specific administration studies.[76] This mechanism of action explains that tapentadol potentiates descending pain inhibition.[77]

Although often regarded as being similar to tramadol, tapentadol differs with regard to its almost complete lack of a serotonergic effect and the fact that metabolites do not contribute to its analgesic effect.[78,79] This explains why no causal relationship between tapentadol and serotonin syndrome has been established and there are no clinically relevant drug interactions between tapentadol and antidepressants.[80]

Efficacy

In settings of osteoarthritis, chronic low back pain, neuropathic pain due to diabetic polyneuropathy and cancer pain, tapentadol provides equianalgesic efficacy to conventional opioids such as oxycodone and morphine, the main comparators.[81-83] This efficacy can be shown across a spectrum of nociceptive and neuropathic pain states as well as mixed nociceptive-neuropathic pain.[84] In neuropathic pain states tapentadol improves neuropathic pain symptoms and quality of life.

Similarly, in contrast to conventional opioids such as oxycodone, tapentadol significantly improves the quality of life of patients with chronic pain due to osteoarthritis and low back pain as shown in a large pre-planned meta-analysis.[81] This effect is seen across most domains of the SF-36 quality of life questionnaire and thereby offers significant outcome advantages in comparison with conventional opioids. In comparative trials, 5 mg oral tapentadol was equianalgesic to 1 mg oxycodone and 1 mg to 3.3 mg morphine.[81,85,86] However, as these are equianalgesic rates and tapentadol has a much lower mu-receptor affinity than conventional opioids, change from a conventional opioid to tapentadol has to be performed slowly over time. Direct immediate opioid rotation leads to opioid withdrawal symptoms. The rotation from tramadol to tapentadol, however, can be performed in one step and leads to better outcomes in most patients.[87]

Safety and adverse effects

In contrast to conventional opioids, tapentadol causes significantly less opioid-induced ventilatory impairment. This has been confirmed in head-to-head comparisons at equianalgesic doses with the conventional opioid oxycodone.[88] More relevantly, data from the US, where tapentadol has been available since 2009, report no fatalities from tapentadol use in a comparative analysis of the safety of various opioids.[89] The same study also showed that tapentadol had the lowest rate of major medical adverse effects, hospitalisations and serious adverse effects of all opioids on the US market, including tramadol. A systematic literature review identified four, possibly five, deaths from single-drug tapentadol overdose worldwide over nine years, which is in stark contrast to, and orders of magnitude lower than, the mortality caused by conventional opioids.[90]

With regard to adverse effects, slow-release tapentadol shows significant less gastrointestinal adverse effects, namely nausea, vomiting and constipation, than the slow-release preparation of the conventional opioid oxycodone.[81] These benefits remained when tapentadol was compared with the slow-release combination of oxycodone and naloxone in another study.[91] The medication is also extremely well tolerated in the elderly, with similar advantages seen in patients aged older than 75 years.[92,93] In a network meta-analysis of the tolerability of opioid analgesics for chronic pain, tapentadol was the top ranking analgesic due to the lowest incidence of overall adverse events, including constipation, and the lowest trial withdrawal rate.[94]

In a three-month study, tapentadol showed significantly less testosterone suppression than oxycodone, with only 11% of patients taking tapentadol compared with 46% of patients taking oxycodone presenting with testosterone levels below the normal range.[91] With regard to effects of tapentadol on immune function, data are currently still sparse, but, in contrast to conventional opioids, short- and long-term tapentadol administration seems to maintain splenic cytokines in animal experiments.[95]

Dependence, abuse potential and diversion

Physical dependence on tapentadol is limited and therefore withdrawal symptoms occur rarely and are mild to moderate, even with abrupt cessation.[96] Tapentadol abuse has been described, but rates are lower than with conventional opioids such as oxycodone, suggesting a significantly lower potential for abuse.[71,97-99] This has been consistently shown for a considerable number of outcome parameters commonly used to identify issues of abuse with a medication.

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An evaluation of the internet discussion among recreational drug users in the US, where tapentadol has been on the market for more than nine years, revealed the lowest proportion of all posts were discussing tapentadol and this was significantly lower by orders of magnitude than any other substance discussed.[99] Endorsement as a drug of abuse for tapentadol was also the lowest and similar to tramadol.

In a post-marketing study of patients assessed for substance-abuse treatment, tapentadol abuse was rare and lower than for most other scheduled analgesics.[98] Tapentadol resulted in significantly lower rates of doctor shopping (obtaining medication from multiple prescribers) than oxycodone.[100] Tapentadol has, together with tramadol, the lowest rate of diversion of opioid analgesics in the US and an extremely low black-market price.[101] These findings in the US have been confirmed in other markets including Australia.

Conclusion

The atypical opioids buprenorphine, tramadol and tapentadol show different profiles to conventional opioids with regard to efficacy, safety, tolerability and risk of abuse. With regard to the specific substances, buprenorphine has the highest mu-receptor effect of the three atypical opioids. This explains why sublingual buprenorphine with higher dosing carries an increased risk of problems found usually with conventional opioids, whereas the low-dose transdermal patch preparation is very safe and has low abuse risk.[6]

Tramadol is not scheduled as a full opioid in most countries of the world (S4, not S8, in Australia) because it was registered before the increased concerns about opioids and carries a relatively low risk of abuse. However, the disadvantages of tramadol are its reliance on a metabolite for its mu-receptor agonist effects and its serotonergic component; these properties make the analgesic effect less reliable and cause a number of adverse effects and drug interactions.

Tapentadol is currently the preferred atypical opioid for the treatment of chronic pain. Tapentadol is equianalgesic to potent conventional opioids and has the most convincing evidence for a positive effect on multiple domains of quality of life.[81] It also has the best tolerability and the lowest rate of fatalities and serious adverse events of all opioids, possibly with the exception of transdermal buprenorphine.[89,94] Finally, its abuse potential is much lower than that of conventional opioids.

It will be interesting to see how a fourth atypical opioid, cebranopadol, currently under development, will compare with these three established representatives of this interesting class of analgesics.[3]

The current literature supports the notion that if opioids are regarded as necessary and useful for the treatment of chronic pain states, atypical opioids should be preferred.[2]

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Use of opioids in chronic noncancer pain

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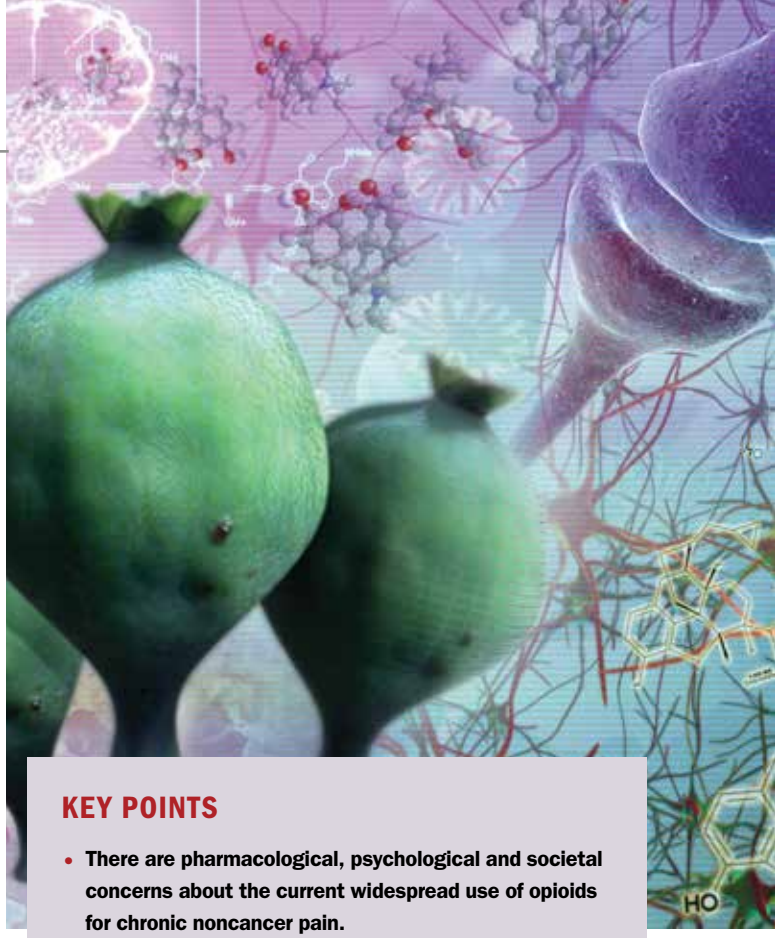
Opioids play a much smaller role in the management of chronic noncancer pain than they do in that of severe acute pain and cancer pain. They are beneficial in a small subset of patients with chronic noncancer pain but there are pharmacological, psychological and societal concerns about their current widespread use for this indication.



KEY POINTS

- **There are pharmacological, psychological and societal concerns about the current widespread use of opioids for chronic noncancer pain.**
- **Opioids should not be regarded as the sole approach to managing chronic noncancer pain but as one component of a multidisciplinary management plan.**
- **They should only be used for this type of pain after an initial trial with defined positive outcomes, in particular improvement of function.**
- **They are not intended as life-long treatment and should be discontinued by tapering the dose when treatment goals are reached (or aberrant drug-taking behaviour becomes obvious).**
- **If a decision to use opioids is made, atypical opioids (transdermal buprenorphine, tramadol or tapentadol) should be used in preference to conventional opioids.**

There has been a dramatic increase in recent years in the use of opioids to treat chronic noncancer pain, particularly in the US but also in Australia. This has led to increasing concerns about the usefulness versus risks of this approach, both for the individual patient and society as a whole. This review article outlines the controversies surrounding their use for treating chronic noncancer pain and summarises their role in this setting, the risks and complications regarding their use for this type of pain and the goals of such treatment, and its initiation and long-term use.

Different pain states

Chronic noncancer pain is a heterogeneous disorder, characterised by a wide spectrum of pain states ranging from physiological pain with nociceptive and inflammatory origin (e.g. osteoarthritis) to pathological pain states of either neuropathic origin (i.e. caused by damage or disease of the somatosensory system, e.g. diabetic polyneuropathy) or dysfunctional origin (i.e. no such damage/disease and no nociception but caused by central sensitisation/insufficient endogenous inhibition, e.g. fibromyalgia).[1] It is therefore not surprising that the role of opioids in these different pain states is not the same.

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Some principles of opioid therapy in the acute pain and chronic cancer pain setting, where they have well accepted analgesic efficacy and a good safety profile, may be transferred to the setting of nociceptive and neuropathic pain, where their use can lead to improved function and reduced pain in some patients, although long-term outcome data are limited or even contradictory.[2,3] Dysfunctional pain states on the other hand are characterised primarily by central sensitisation and limited endogenous inhibition, and seem to be poorly responsive to opioid therapy. Furthermore, chronic pain is characterised as a sociopsychobiomedical phenomenon, and the wide array of psychosocial factors, such as catastrophising, anxiety, mood states including depression, suffering and dependence on the healthcare system, are not really responsive to opioids and need to be addressed by multimodal, multidisciplinary interventions.[4] Single modality opioid therapy in dysfunctional pain states is both less successful in improving analgesia and functional outcome and also carries a

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significant risk of aberrant drug-taking behaviour and abuse.

Efficacy

As indicated above, opioids might confer a benefit and have some demonstrated efficacy in well-defined chronic pain states such as osteoarthritis and neuropathic pain.[5-8] Despite opioids showing effectiveness and published guidelines supporting their use in osteoarthritis-related pain, a 2009 Cochrane review on the efficacy of opioids in osteoarthritis of the knee or hip found only small-to-moderate beneficial effects of opioids and an increased risk of adverse effects.[2,9,10] Similarly, opioids are viewed in guidelines for neuropathic pain treatment as second- or third-line treatments because of their risk-benefit profile,[11-13] and therefore should only be used if first-line drugs (such as anticonvulsants and antidepressants) fail or are contraindicated.

The overall evidence for efficacy of opioids in chronic noncancer pain is even more disappointing. A 2010 Cochrane review on long-term opioid management of chronic noncancer pain that included a total of 4893 patients found only weak evidence for sustainable pain relief and an inconclusive benefit on functional improvement or quality of life.[14] A similar outcome in relation to lack of improved pain control, function or quality of life in chronic noncancer pain patients treated with opioids was reported in a large epidemiological study from Denmark.[15]

In summary, the evidence in favour of use of opioids in the chronic noncancer pain setting is at best weak. This statement is further confounded by most trials assessing only short-term benefits, having methodological flaws and describing heterogeneous outcomes.

Risks and complications of opioid therapy

The most serious complication of opioid use is opioid-induced ventilatory impairment leading to death. Although this is unlikely to occur in patients who are taking a stable dose of opioid for long-term treatment, statistics for the US and Australia show a dramatic increase in mortality linked to prescription opioids.[16,17] Reasons for this increased mortality include incorrect opioid prescribing by doctors and incorrect intake by patients, and also diversion with use by others and coadministration with sedatives such as alcohol and benzodiazepines.[18]

Constipation is a major adverse effect of the long-term use of opioids and seriously affects patients' quality of life. Patients do not develop tolerance to opioid-induced constipation and need co-medication with appropriate laxatives. Opioid preparations with a reduced risk of constipation are transdermal patches or combinations with naloxone.[19] Nausea, vomiting, sedation and cognitive impairment are often only short-term adverse effects; tolerance to these can develop and therefore interference with work or driving as well as the increased risk of falls occur primarily in periods of dose titration or dose escalation.[20,21] Opioids, via direct effects on the mu-receptor, also cause significant impairments of immune and endocrine functions, particularly with long-term use. Impairment of endocrine function can lead to opioid-induced androgen deficiency requiring testosterone substitution.[18]

The phenomenon of opioid-induced hyperalgesia, a paradoxical increase in sensitivity to pain in patients on long-term opioid therapy, should also be mentioned.[22] Attempts to treat this with increasing opioid doses can result in escalation of opioid doses without benefit for the patient.[18] This therefore needs to be differentiated from development of tolerance to opioids.[23] Physiological dependence will also develop, but it and the potential withdrawal reactions can be overcome by tapering opioid doses slowly instead of discontinuing abruptly.

There are rather contradictory and inconsistent data on the prevalence of opioid abuse in patients using opioids for chronic noncancer pain. Addiction ('psychological dependence') is a behavioural pattern of drug use, characterised by overwhelming involvement with the use ('compulsive use') of a drug leading to physical, social and psychological harm.[24] A systematic review of trials of opioid therapy for chronic back pain showed a prevalence of lifetime substance abuse in the order of 36 to 56% and of current aberrant medication use of 5 to 24% in these patients.[25] Similarly, in a recent study, one in three patients undergoing long-term treatment with opioids for chronic pain met *DSM-IV* criteria for addiction.[26] On the other hand, a Cochrane review from 2010 reported an addiction rate of only 0.27% in patients undergoing long-term opioid therapy for chronic noncancer pain.[14] Risk factors for the development of addiction are male gender, younger age, history of substance abuse disorder, mental health problems and use of higher doses of opioids.[26,27]

Finally, there is a risk that long-term opioid therapy might contradict the goals of chronic pain management. These goals are not only pain reduction but also reduced pain behaviour, improved function and increased self-efficacy. Current data suggest that opioids are used particularly to treat patients who describe greater disability, distress and suffering and poorer functioning, which might set up a vicious cycle.[25] Rather than promoting self-efficacy and an internalised locus of control, opioid therapy leads to an externalised locus of control with increased dependence on the healthcare system, encouragement of passivity and reinforcement of pain behaviour proven to be counterproductive in patients with chronic pain.[28]

1. OPIOID THERAPY: USEFUL REFERENCE MATERIAL

- Quick clinical guidelines for the use of opioids in patients with chronic noncancer pain, which originated in WA and Queensland: www.health.qld.gov.au/__data/assets/pdf_file/0032/374693/ddu_quick_guide.pdf
- A more detailed prescription opioid policy, agreed upon by the Faculty of Pain Medicine of ANZCA, the RACGP, RACP and RANZCP: http://fpm.anzca.edu.au/documents/prescription-opioid-policy.pdf
- Examples of treatment contracts for an opioid medicine: www.aci.health.nsw.gov.au/__data/assets/pdf_file/0018/212760/Opioid_treatment_agreement.pdf; OR www.racgp.org.au/your-practice/guidelines/drugs-of-dependence-a/appendix-d-example-practice-policies/D5-Practice-policy---Drugs-of-dependence-therapy-agreement

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2. OPIOID THERAPY: FACTORS TO CONSIDER BEFORE INITIATION*

- Pain diagnosis/psychological assessment
- Multidisciplinary pain treatment
- Assess baseline function and severity of pain
- Screen for addiction risk
- Determine treatment goals (focus on functional and quality of life improvement)
- Explain risks and benefits of opioid therapy
- Opioid treatment contract with patient: informed consent, rules for treatment and cessation, consequences of aberrant drug-taking behaviour

* Modified from multiple sources including references 3, 18 and 30.

Implementation of opioid therapy

The basis of good chronic pain management is a multidisciplinary and multimodal approach. Psychological therapy with emphasis on cognitive behavioural strategies to enhance coping mechanisms and reduce psychological stressors and physical therapy that includes exercise programs and physiotherapy form integral components of such an approach. Pharmacological therapy should be initiated according to well-established guidelines, with paracetamol and NSAIDs/cyclo-oxygenase (COX)-2 inhibitors being used in nociceptive pain states and anticonvulsants and/or antidepressants in neuropathic pain states. As a small subgroup of patients with chronic pain may benefit from opioid use, this treatment should not be denied. However, in view of the risks described above, the introduction of opioids to treat chronic non-cancer pain requires strict adherence to well-established guidelines.[29,30] Details of examples of a quick clinical guideline for the use of opioids in patients with chronic noncancer pain, a prescription opioid policy and a treatment contract for an opioid medicine are given in Box 1.

Opioids should not be considered as a first-line treatment or a single treatment modality but as one component of multidisciplinary pain treatment. They should only be trialled after reasonable attempts at multidisciplinary pain management, including other pharmacological options, have failed. Their introduction requires a diagnosis of persistent nociceptive-inflammatory pain (e.g. osteoarthritis) or neuropathic pain, and even then they should only be considered second- or third-line treatment.[18,31] They should not be used in dysfunctional pain states, including fibromyalgia, visceral and pelvic pain syndromes, headaches and nonspecific chronic low back pain. Factors to be taken into account before initiation of opioid therapy are listed in Box 2.

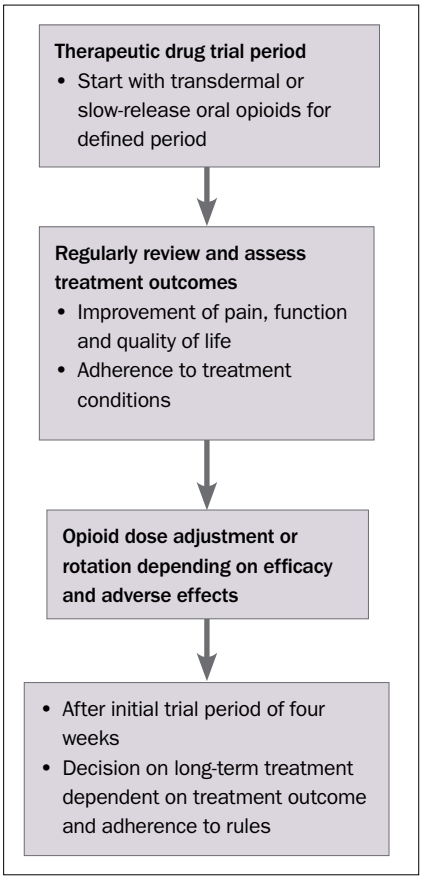

Figure 1. Initiation of opioid therapy.

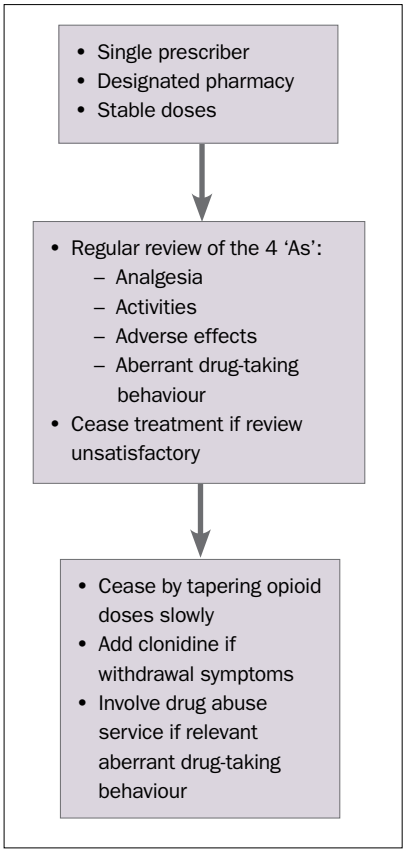

Figure 2. Long-term treatment/maintenance opioid therapy.

Initiation of opioid therapy for chronic non-cancer pain should be in the form of a closely monitored trial period of about four weeks' duration of a transdermal or slow-release oral opioid. Atypical opioids (i.e. transdermal buprenorphine or slow-release tramadol and tapentadol) are the preferred opioids in this setting.[32] In comparison to conventional opioids, they have better effects on function and quality of life and reduced risks of abuse, diversion and overdose fatality.[33] Definitive endpoints such as improvement in quality of life and function, including mood, sleep, occupational and recreational activities, should be as important as simple pain reduction. Such endpoints along with risks, benefits and rules on supply should ideally be formulated as an opioid contract between the patient and the provider. Failure to achieve these treatment goals on reasonable opioid doses (less than 100 mg daily oral morphine equivalent) deems the patient's pain as not responsive to opioids and should lead to an agreed termination of opioid treatment via tapering doses. An approach to the initiation of opioid therapy is summarised in Figure 1.

If the agreed endpoints were reached, the patient should qualify for long-term treatment with opioids; however, this should not be seen as a decision for life-long treatment. Long-term treatment requires adherence to the opioid contract,

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including a single prescriber, a designated pharmacy and no unauthorised escalation of doses. Regular monitoring of the patient should assess the four 'As' of pain treatment outcomes: Analgesia, Activities of daily living, Adverse effects and Aberrant drug-taking behaviour. An approach to long-term opioid therapy is summarised in Figure 2.

Indications for cessation of long-term opioid therapy are lack of improvement in function, lack of analgesia and aberrant drug-taking behaviour.[18,31]

Conclusion

Opioids play a much lesser role in the management of chronic noncancer pain than they do in the management of severe acute pain and cancer pain. Although they may be beneficial in a very small subset of patients with chronic noncancer pain, who should not be denied treatment of their chronic condition, there are pharmacological, psychological and societal concerns about their current widespread use for this indication. Their use in the management of chronic noncancer pain requires an established pain diagnosis, screening for increased risk of abuse, a good doctor-patient relationship and adherence to agreed rules, ideally formulated in a treatment contract and preference of atypical opioids over conventional opioids. Opioids should only be used after an initial trial with defined positive outcomes, in particular improvement of function; a failed trial should lead to discontinuation by tapering the opioid dose.

Opioids should never be regarded as the sole approach to chronic noncancer pain but as one component of a multidisciplinary management plan. Even if used with benefits, they are not intended as life-long treatment and should be weaned when function has been stabilised (or aberrant drug-taking behaviour becomes obvious). This might be a particular challenge in the many patients who have been started on opioids inappropriately in the past. PMT

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Acute and chronic musculoskeletal pain

Pharmacological management

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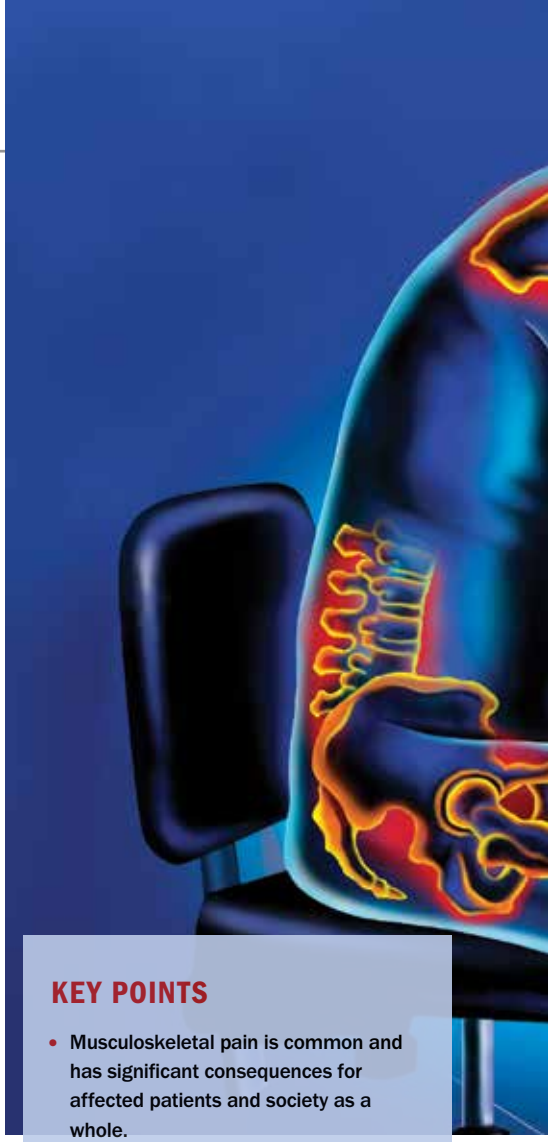
A multimodal, multidisciplinary approach is required when managing patients with musculoskeletal pain. Nonopioid analgesics should be trialled first and opioids then used with caution.



KEY POINTS

- Musculoskeletal pain is common and has significant consequences for affected patients and society as a whole.
- Musculoskeletal pain is not purely nociceptive; peripheral inflammation and central sensitisation processes, as well as neuropathic components, contribute.
- Management of patients with these conditions should be multimodal and multidisciplinary, not rely on pharmacological approaches alone, and follow principles of chronic disease management aiming for improved function.
- Nonopioid analgesics, in particular NSAIDs, play an important role in the pharmacological management of patients with these conditions.
- Opioids should be used with caution and only after careful consideration in patients with musculoskeletal pain; tramadol, buprenorphine and tapentadol may be preferable.
- Adjuvants such as anticonvulsants (e.g. pregabalin) and antidepressants (e.g. duloxetine) may play a previously underestimated role in the management of patients with musculoskeletal pain.

Musculoskeletal pain is a major burden on the psychosocial and physical wellbeing of an individual. In 2015, musculoskeletal conditions were the most common chronic disorders in Australia and were largely managed in the primary care setting. According to self-reported estimates in 2011 to 2012, 28% or 6.1 million people in Australia experienced chronic musculoskeletal conditions, mainly arthritis.[1] Of these, 14% had back pain, 8% chronic osteoarthritis (OA), 3% osteoporosis and 2% rheumatoid arthritis. Previous estimates have suggested that $5.7 billion was spent on patients with chronic musculoskeletal problems in Australia from 2008 to 2009. This included the costs of pharmacological treatments and joint replacements.[1]

Musculoskeletal pain is caused by conditions of the bones, muscles and their attachments (i.e. tendons, ligaments and connective tissues), and arthritis (i.e. joints).[1,2] These conditions range in time frame from sudden-onset and short-lived problems to life-long chronic disorders. Consequences of the pain include loss of dexterity and mobility, which explains why musculoskeletal conditions are the most common cause of disability.[2]

It is estimated that 20% of primary care visits are due to musculoskeletal disorders, and many practitioners feel uncomfortable managing patients with common problems associated with these conditions.[3] The issues of managing affected patients are further compounded by the fact that most are elderly with significant comorbidities and increased risk of adverse effects of medications. Most importantly, thorough clinical assessment and investigations for underlying medical disease or chronic inflammatory conditions

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should be performed to avoid missing other diagnoses or stereotyping patients.[4]

Common approaches to managing patients with musculoskeletal pain include several pharmacological and nonpharmacological treatments, including pharmacotherapy, surgery, injections, physical therapy, psychological approaches such as hypnosis, relaxation and cognitive behavioural therapy, and complementary or alternative medicines. Improved understanding of pain physiology and the underlying neurobiology has improved patient outcomes through the development of new approaches, better analgesics and more advanced delivery techniques.

Mechanisms of pain

Early concepts focused on degenerative wear and tear of the musculoskeletal elements as the main underlying mechanism of musculoskeletal pain, with inflammatory factors leading to peripheral sensitisation. However, more recent data suggest that central sensitisation and, in particular, neuropathic elements also play a significant role in the background of musculoskeletal pain.[5]

For example, it is widely accepted that in the joint, peripheral unremitting inflammatory reactions cause peripheral sensitisation, especially after an acute injury. Different types of mechanoreceptors in the joint, including polymodal type IV receptors, are involved in local sensitisation as seen in inflammatory conditions.[6] Furthermore, subsequent central neuronal plasticity causes perpetuation of pain; this process is now commonly called central sensitisation.[7] Functional MRI studies (fMRI) and psychophysical quantitative sensory testing (QST) confirm that increased activity in the central nervous system is associated with skin stimulation in patients with chronic OA.[6,8] Pain signal amplification in the central nervous system augments pain perception leading to allodynia (non-noxious stimuli perceived as pain) and hyperalgesia (heightened response to painful stimuli). Clinically, patients with dominant features of central sensitisation experience disproportionate pain, fatigue, cognitive impairment and other somatic symptoms such as sleep deprivation, stress and anxiety. Features of central sensitisation can be identified by the use of the Central Sensitisation Inventory, which can then guide clinicians in selecting the most appropriate therapeutic approaches.[9] Similarly, components of neuropathic pain can be identified using screening questionnaires, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale, the Douleur Neuropathique 4 (DN4) or the painDETECT questionnaire.[10]

Nonopioid analgesics

Paracetamol

Paracetamol has no specific endogenous binding sites, hence the continuous debates surrounding its mechanisms of action.[11] It seems to exert effects centrally, possibly via direct and indirect cyclo-oxygenase inhibition; the activation of spinal serotonergic and endocannabinoid systems also appears to be involved in its analgesic effect.

When used by patients with acute postoperative pain, paracetamol is an effective analgesic, with an NNT50% in the range of 3.6; that is, 3.6 patients need to be treated to achieve 50% pain reduction involving one patient compared with placebo.[12] However, the results are much more disappointing in patients with musculoskeletal pain conditions. A large randomised trial in patients with acute back pain showed no benefit of regular or on-demand paracetamol on pain relief and time to recovery compared with placebo.[13] Similarly, a meta-analysis of paracetamol use in patients with chronic low back pain showed no beneficial effect on pain, function or quality of life.[14] In the same meta-analysis, paracetamol improved pain and disability in patients with OA of the hip and knee; however, although the effects were statistically significant, they were too small to be clinically important. These disappointing findings were confirmed in another network meta-analysis of pharmacological interventions in patients with OA of the knee; of all interventions analysed, paracetamol showed the poorest improvement, the only one that was not clinically meaningful.[15] Although this does not mean that paracetamol may not be useful in patients who respond well to it, it leads to a reconsideration of most previous guidelines emphasising the role of paracetamol as first-line treatment in the setting of acute and chronic musculoskeletal pain.[16]

Paracetamol combined with an NSAID is superior to either compound alone; this has been shown in particular for the combination of paracetamol and ibuprofen, available commercially.[17,18] Similarly, the combinations of paracetamol with a weak opioid such as codeine or tramadol are more effective than paracetamol on its own, shown mostly in patients with acute postoperative pain.[19,20] There are also some data on the efficacy of paracetamol and tramadol combinations in patients with chronic musculoskeletal pain.[21]

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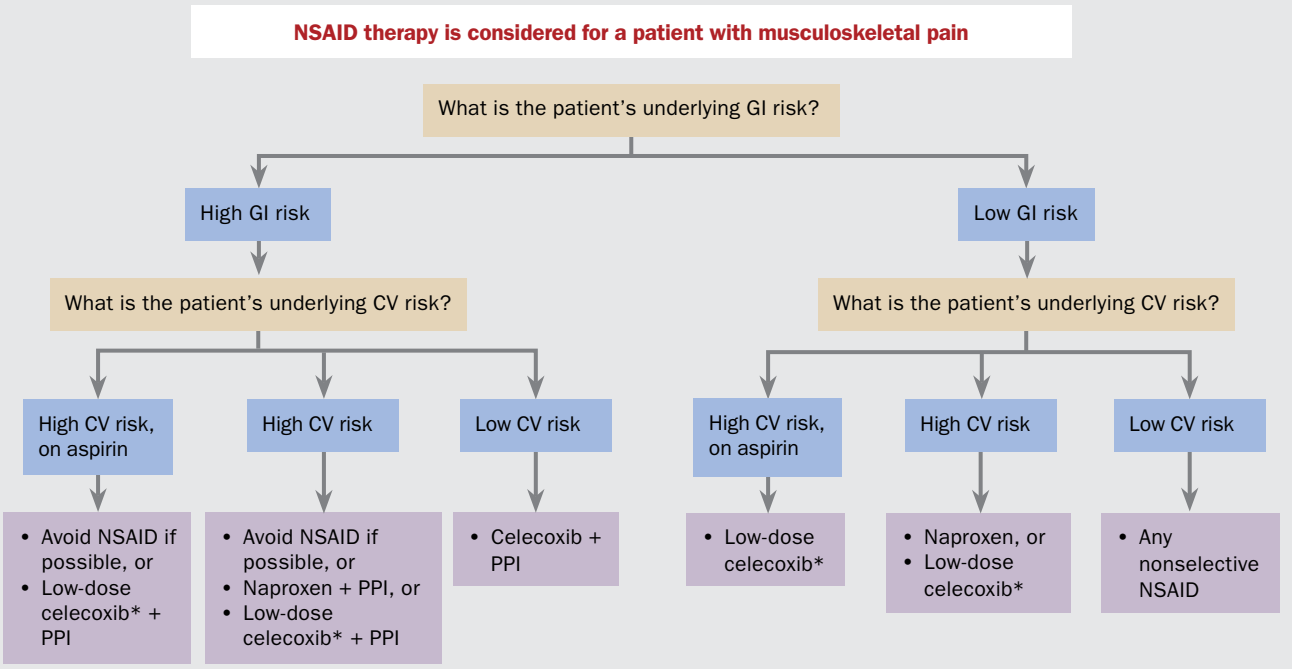
AN APPROACH TO LONG-TERM NSAID THERAPY FOR MUSCULOSKELETAL PAIN



Abbreviations: CV = cardiovascular; GI = gastrointestinal; PPI = proton pump inhibitor.
* Low-dose celecoxib is 200 mg daily.
Adapted from BMC Med 2015; 13: 55.[22]

Systemic NSAIDs

The biological stress response that occurs after a trauma or surgery generates chemical mediators such as prostaglandins, which contribute to acute pain and its morbidities. A low-grade local or systemic inflammation may persist, explaining the more complex pathophysiology of persistent or chronic pain conditions.[22,23] As such, NSAIDs represent a sensible strategy for treating patients with acute and chronic musculoskeletal pain.

NSAIDs have an established analgesic efficacy in the treatment of patients with acute postoperative pain.[16] They are also similarly effective in the treatment of those with chronic low back pain and acute ankle sprain.[24] In patients with OA, NSAIDs provide clinically meaningful analgesia superior to paracetamol and comparable with opioids.[15,25] There seems to be no difference in efficacy between appropriate doses of nonselective NSAIDs (nsNSAIDs) and the selective NSAIDs, cyclo-oxygenase (COX)-2 inhibitors.

The main concerns with short- and long-term use of nsNSAIDs are upper and lower gastrointestinal (GI) events (i.e. ulceration, bleeding, perforation or NSAID enteropathy), risks of cardiovascular (CV) events and renal impairment.[26] Adverse renal effects increase in patients with pre-existing renal impairment, hypotension, hypovolaemia, concurrent use of nephrotoxic drugs and multiple NSAID use. Risks of upper GI problems follow long-term and short-term use of nsNSAIDs.[24]

COX-2 inhibitors selectively inhibit the inducible isoenzyme COX-2, preserving function of the constitutional isoenzyme COX-1, which determines protective functions of prostaglandins, in particular in the GI tract. Therefore, COX-2 inhibitors show reduced GI adverse effects compared with nsNSAIDs.[27] Upper GI events due to nsNSAIDs are relatively reduced when combined with proton pump inhibitors (PPI) in susceptible patients, but PPIs are not protective for NSAID enteropathy.[22] Compared with the COX-2 inhibitor celecoxib, the nsNSAID diclofenac plus a PPI caused more clinically significant upper and lower GI events.[28] The best gastroprotective combination in high-risk patients who had previous GI bleeding is a COX-2 inhibitor plus a PPI.[29]

In terms of CV risk, naproxen seems to be associated with less harm from CV events compared with other nsNSAIDs.[30] However, celecoxib may have a similar rate of CV effects[27] and may be an alternative to naproxen with reduced GI adverse effects.[22] The Flowchart shows a risk-based algorithm for the selection of the most appropriate NSAID in various risk situations.[22]

Even in patients with acute renal failure, COX-2 inhibitors may be advantageous over nsNSAIDs. In a large case-control study, the risk of renal impairment was

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shown to increase with a decrease in cyclo-oxygenase selectivity, favouring the use of COX-2 inhibitors.[31]

Elderly populations are at increased risk of adverse events from NSAIDs. However, in a large retrospective study of an elderly cohort in the USA, risks of falls, fractures and hospital admissions were lower with nsNSAID and COX-2 inhibitor use than with opioid use.[32] Overall, all NSAIDs showed a reduced relative risk of safety events including mortality, challenging the notion that opioids are safer in this age group.

Topical NSAIDs

Topical NSAIDs are effective for the treatment of patients with short-term exacerbation or acute attacks of localised pain, such as strains, sprains or sports injuries, which often occur in the setting of chronic musculoskeletal pain. Application of a topical gel of ketoprofen, ibuprofen, diclofenac and piroxicam, but not indomethacin, two to three times daily provides effective pain relief with systemic adverse effects comparable with placebo.[33] Similarly, topical diclofenac and ketoprofen can provide pain relief in individuals with chronic pain due to OA with adverse effects comparable with placebo.[34] Topical rubefacients containing salicylates seem not to be effective in people with acute and chronic conditions.[35]

Opioids

There is a worldwide ongoing debate on the use of opioids for the treatment of people with chronic pain of nonmalignant origin.[36] Issues are the limited efficacy in this setting as well as problems with aberrant use, abuse and diversion. The resulting epidemic of prescription opioid overdoses with an unacceptably high mortality in the USA[37] and also in Australia[38] suggest that a more cautious approach to opioid use is required. In addition, chronic opioid use seems to relegate self-efficacy and promote an externalised locus of control, leading to further dependence on the healthcare system thereby contradicting the functional goals of pain management.[39] Therefore, evidence-based guidelines, for example in elderly patients with chronic musculoskeletal pain, recommend chronic opioid therapy only with great caution and when all other safer alternatives have not been effective or not suitable.[40] Use of opioid risk assessment tools to identify patients at risk of aberrant drug-related behaviours should be considered.[41]

Specifically, in patients with chronic pain due to OA, strong opioids have not been found to be more effective than NSAIDs[25] or, in some studies, than placebo.[42] At the same time, use of opioids resulted, as outlined above, in more falls, fractures, hospital admissions and mortality than NSAID use in this high-risk elderly population.[32] Other adverse effects, which need to be considered when using opioids in the long term include opioid-induced androgen deficiency (leading to decreased testosterone levels and subsequent osteoporosis), immune suppression and opioid-induced hyperalgesia, paradoxically increasing pain levels.[36]

Controlled-release preparations or long-acting opioids are usually recommended for prolonged treatment in patients with chronic pain; however, recent guidelines issued by the Centers for Disease Control and Prevention (CDC) question this rationale. No evidence was found that continuous administration of controlled-release opioids is more effective or safer than intermittent use of immediate-release opioids or reduces opioid misuse or addiction.[43] If controlled-release preparations are used, then abuse-deterrent formulations such as a slow-release oxycodone preparation should be chosen.[44]

Specifically, transdermal buprenorphine and, even more so, the atypical centrally acting analgesics tramadol and tapentadol may offer some advantages in the chronic pain setting.

Transdermal buprenorphine

Transdermal buprenorphine is widely used in the setting of chronic musculoskeletal pain, particularly in elderly patients. One advantage with using transdermal buprenorphine is the option of starting at a very low dose of 5 mcg/h. Furthermore, buprenorphine shows a ceiling effect for respiratory depression but not analgesia with increasing doses, which might increase its relative safety;[45] other advantages are less constipation, immune and androgen suppression. Last, but not least, it might cause less tolerance and hyperalgesia than other opioids.[46]

Buprenorphine patches at doses of 5 to 20 mcg/h were reported as being effective or very effective with high treatment adherence in a recent UK observational study in patients with chronic musculoskeletal pain.[47] The results were comparable with those seen with sustained-release tramadol in patients with musculoskeletal pain who had had no relief with nsNSAIDs.[48] Buprenorphine patches were also successfully trialled in multimorbid patients with significant analgesic efficacy and tolerable adverse effects.[49]

Atypical centrally acting analgesics: tramadol and tapentadol

Tramadol is classified as an atypical centrally acting analgesic. Its opioid effects are from an active metabolite (M1) and its more important analgesic efficacy results from noradrenaline and serotonin reuptake inhibition. This mechanism of action leads to improved analgesia with reduced opioid side effects such as constipation and a lower risk of respiratory depression and abuse.[50] It has been used with benefit in patients with OA.[51,52] However, disadvantages of tramadol include serotonergic adverse effects such as nausea and vomiting, potential interactions with other serotonergic drugs (e.g. antidepressants) and the reliance on the opioid effect of a metabolite. The metabolic pathway to this metabolite is via cytochrome (CYP) 450 2D6 and is thereby dependent on the specific phenotype for this enzyme in an individual patient.[53]

The recently registered tapentadol overcomes most of these disadvantages because the molecule itself is an opioid agonist with 18 times less affinity to human mu-receptors than morphine and strong noradrenaline reuptake inhibition with negligible effects on serotonin.[54,55] Despite the weak opioid

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agonism, it can match the analgesic efficacy of morphine in a 3:1 (tapentadol to morphine) dose ratio and oxycodone in a 5:1 (tapentadol to oxycodone) dose ratio.[56]

In patients with chronic low back pain or OA, a meta-analysis showed that the analgesic effect of slow-release tapentadol was noninferior to that of slow-release oxycodone.[56] However, improvement of quality of life measures were superior in the tapentadol group, which experienced significantly lower rates of GI adverse effects (i.e. nausea, vomiting, constipation) and fewer treatment discontinuations. These results were confirmed in a network meta-analysis against several other conventional opioids (i.e. fentanyl, hydromorphone, morphine and oxymorphone).[57] Also, data from the USA so far suggest a significantly lower risk of abuse than with conventional opioid use.[58]

Symptomatic slow-acting drugs for osteoarthritis

Guidelines from the European League against Rheumatism (EULAR) for managing patients with pain due to knee OA suggest compounds such as glucosamine and chondroitin sulfate should be used as an initial approach.[59] A recent consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) reiterated a similar endorsement. It placed a particular emphasis on the use of a patented prescription formulation of a crystalline glucosamine and chondroitin sulfate combination, for which high-quality evidence of its efficacy compared with other formulations was provided.[60,61]

Adjuvants

With the recognition that central sensitisation and elements of neuropathic pain contribute significantly to chronic musculoskeletal and joint pain comes the development of a new role for antidepressants and anticonvulsants in the management of patients with these pain conditions.[6] For example, pregabalin is now indicated for neuropathic pain and duloxetine for diabetic polyneuropathy. The beneficial effects of tramadol and tapentadol due to their noradrenergic effects, described above, apply also to antidepressants, thereby strengthening descending pathways of pain inhibition.[62]

Antidepressants

Duloxetine is a serotonin and noradrenaline reuptake inhibitor (SNRI) antidepressant, which has been extensively studied for use in patients with neuropathic pain regardless of its disease origin; it is here recommended as a first-line treatment, although it is only indicated for diabetic peripheral neuropathic pain and chronic musculoskeletal pain.[63] In patients with chronic knee OA and chronic low back pain, duloxetine is effective compared with placebo, with significant improvement seen in physical outcomes.[64,65] With the accumulating evidence for its efficacy, duloxetine has been included in the recently updated Osteoarthritis Research Society International (OARSI) guidelines for the nonsurgical management of patients with chronic OA.[66] Commonly observed adverse effects of duloxetine are nausea, fatigue and constipation.[67,68]

Other SNRIs such as venlafaxine and tricyclic antidepressants (TCAs) such as amitriptyline may be useful in managing patients with neuropathic pain (off-label uses); but there are no studies to support their use in patients with musculoskeletal pain. Furthermore, TCAs are best avoided in the elderly because their anticholinergic activity increases the cumulative risk of cognitive impairment and mortality in this age group.[69]

Anticonvulsants

The anticonvulsants recommended as first-line treatment for patients with neuropathic pain are gabapentin and pregabalin.[63] As modulators of the alpha-2 delta subunits of voltage-gated calcium channels in the central nervous system, they diminish neuronal calcium influx and reduce release of excitatory neurotransmitters, primarily glutamate, and thereby reduce central sensitisation.[70] They are, therefore, effective in treating patients with fibromyalgia (off-label uses).[71]

In one randomised controlled trial in patients with knee OA, pregabalin was found to be as effective as meloxicam and the combination of both was superior to each individual component with regard to pain and improvements in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score.[72]

Overall principles of pharmacological management of musculoskeletal pain

The aim of medication use for pain control is always to facilitate initiation of daily activities and break the cycle of persistent pain, which leads to fear-avoidance and subsequent musculoskeletal deconditioning. Therefore, when managing musculoskeletal pain in particular, the emphasis should be on the ultimate goal of improved function. Pharmacological therapy should never be used alone, but integrated into multimodal and multidisciplinary management of the sociopsychobiomedical features of chronic pain and is only one component of such management.[73] This approach requires a stepwise integration of broad modalities of nonpharmacological and pharmacological treatments, based on prioritisation of intervention.[61,74]

Conclusion

A therapeutic approach to musculoskeletal pain requires an understanding of the underlying pathophysiology, but also a detailed exploration of the impact on the individual patient's life and therapeutic goals. Nonpharmacological approaches, in particular physical therapies and psychological management, are an important component of such an approach. Pharmacological treatments can and need to complement these approaches with the ultimate goal of improving a patient's daily function and quality of life.

In chronic pain states, long-term continuation of pharmacological treatments has to be balanced against their potential adverse effects and complications. The

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recent recognition of elements of neuropathic pain and central sensitisation contributing to musculoskeletal pain states has opened new therapeutic avenues. MT

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Tapering off opioid analgesia

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Opioids are being increasingly used for treating chronic noncancer pain but adverse events outweigh the benefits of long-term opioid treatment in these patients. As abrupt cessation of opioid analgesia can lead to unpleasant withdrawal symptoms, tapering off opioid therapy is the preferred strategy.

The past 20 years have seen an unprecedented expansion in the use of opioid analgesics in Australia, with opioid dispensing episodes increasing by at least 15-fold.[1] One of the most important changes in clinical practice during this period has been the long-term use of opioid analgesics in treating chronic noncancer pain. Although the efficacy of opioids for short-term pain relief from acute pain conditions and the necessity of their regular use in the treatment of cancer pain has been well established, there is insufficient evidence for the long-term benefits of opioid analgesia in the treatment of chronic noncancer pain.

Almost half of the opioids prescribed in general practice are for chronic noncancer pain.[2] Increased patient awareness of and demand for the right to pain relief, along with ongoing problems of access to multidisciplinary chronic pain management services, may be adding to the over-reliance of GPs on opioid analgesia when treating this type of pain.

There are almost 250 preparations of opioid analgesics on the market in Australia, leading to aggressive marketing strategies. These strategies potentially contribute to the overuse of opioid analgesics for treating chronic noncancer pain in the time-constrained setting of general practice, where prescribing a pain killer for a pain problem may be the expected clinical outcome for all involved. It is also important to acknowledge that both undergraduate medical training curricula and vocational GP training curricula in Australia lack a focused pain management component.

There is a consensus that adverse events outweigh the benefits of long-term opioid treatment.[3] Misuse of, dependence on and addiction to these medications present an alarming public health problem in Australia. A major concern is the recent upsurge in serious harms associated with opioids, particularly the substantial increases in opioid-related hospitalisations and death rates.[1] Hospitalisations related to pharmaceutical opioids now outnumber those related to heroin use in Australia.[1]

In patients for whom the long-term use of opioid analgesics is problematic, due to either adverse effects or aberrant behaviour, abrupt cessation is not an ideal option because of the associated withdrawal symptoms (Box 1). Tapering off these medications is an alternative strategy that can prevent discomfort and complications related to withdrawals.

This article provides a practical overview of best practice for tapering opioid therapy in the general practice setting.

KEY POINTS

- The long-term use of opioids for analgesia in patients with chronic noncancer pain is associated with health and social problems.
- Ceasing opioids abruptly after prolonged use may cause withdrawal symptoms.
- Tapering opioids may improve mood and function as well as pain outcomes.
- A structured tapering program can prevent an unpleasant withdrawal experience for the patient.

Indications for tapering

There are many valid reasons to consider tapering a patient's opioid analgesics, including the following:

- the patient may decide that they do not want to be taking any medication
- the side effects of an opioid medication may be intolerable (Box 2)
- despite regular dose increases, opioids may not be yielding the desired pain relief and functional outcomes
- the patient's condition may improve to a level where the pain medication is no longer necessary
- the patient may be misusing the medication or exhibiting aberrant drug-related behaviour.[4]

An appropriate specialist's input and further attention may be required in planning and conducting the tapering process in some clinical situations.

- **Unstable medical and psychiatric conditions.** As opioid withdrawal is associated with anxiety and insomnia, if the patient has a condition that would be worsened with anxiety, such as a poorly-controlled arrhythmia or untreated mood disorder, it is essential

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1. SIGNS AND SYMPTOMS OF OPIOID WITHDRAWAL

- Drug craving
- Anxiety
- Insomnia
- Abdominal pain
- Vomiting
- Diarrhoea
- Diaphoresis
- Mydriasis
- Tremor
- Tachycardia
- Piloerection

to deal with these problems first.

- **Concomitant sedative medications.** It is best to avoid the use of sedatives during opioid tapering; however, if there is a clinical indication for these medications, staged dispensing might help reduce the risk of overdose.
- **Pregnancy.** Severe, acute opioid withdrawal has been associated with premature labour and spontaneous abortion, especially during the first trimester. Specialist advice should be sought or relevant guidelines referred to before tapering in pregnant women.[5]
- **Polysubstance use or access to opioid medications from other sources.** These patients are best managed in consultation with addiction services, possibly within a substitution treatment framework involving methadone or buprenorphine. An inpatient admission to a residential drug and alcohol facility may be warranted if the polysubstance use (especially the use of other sedating agents) is prominent.

Preparation for tapering

As soon as a valid indication for tapering of opioid analgesics is established, it is important to have a conversation with the patient to explain the process and develop a treatment agreement. This agreement could include:

- time frame for the agreement
- goals of the taper
- agreed frequency of dose reduction
- requirement for obtaining the prescriptions from a single clinician and a named pharmacy
- scheduled appointments for regular review
- expected effects of the taper
- disallowing increasing the medication dose without first discussing it with the prescriber
- consent for urine drug screening
- possible consequences of not following the treatment agreement.

Before starting tapering, it needs to be clearly emphasised to the patient that reducing the dose of opioid analgesia will not necessarily equate to increased pain and that it will, in effect, lead to improved mood and functioning as well as a reduction in pain intensity. The prescriber should establish a therapeutic alliance with the patient to develop a shared and specific goal. For example, a patient may decide to withdraw completely from opioids by the end of the year. The prescriber can advise clinically appropriate goals. In some cases, the goal might be to reduce the dose to a certain level if the patient cannot completely withdraw from the medication.

The prescribing of opioid analgesia for a prolonged period (usually more than eight weeks) on a regular basis is regulated by state and territory health authorities in Australia.[6] It is important that the prescribing doctor is familiar with the regulation in their state or territory and that the parameters surrounding prescribing practice are clearly discussed with the patient.

Principles of tapering

To improve patient safety and achieve a practical positive outcome, consolidating all opioid analgesia into a single long-acting agent is recommended.[5] The main objective of tapering is to reduce the dose of medication at an interval that will not cause any withdrawal symptoms.

Type of opioid, dosing and dispensing schedule

Unless there is a contraindication, the RACGP guidelines recommend all patients beginning opioid tapering be switched to controlled-release morphine tablets.[5] For converting any opioid analgesic dose to the appropriate dose of oral morphine, the general principle is to calculate the total daily morphine-equivalent dose by using a conversion table (e.g. see opioid calculators in Box 3), then starting at half of this calculated dose of oral, controlled-release morphine, with a view to adjusting the dose to avoid withdrawal or sedation. It is important to choose the timing of this opioid

2. SIDE EFFECTS OF OPIOIDS

Common

- Sedation
- Dizziness
- Nausea
- Vomiting
- Constipation
- Tolerance
- Physical dependence
- Addiction
- Respiratory depression

Less common

- Hyperalgesia
- Delayed gastric emptying
- Hormonal dysfunction
- Muscle rigidity
- Myoclonus

rotation so that a dose review in three to four days is possible for both patient and prescriber. If prescribers do not feel confident about opioid rotation (switching from one opioid to another), they can contact their local pain management centre for further advice.

Prescribing scheduled doses is potentially more helpful for the patient than prescribing as required, as it provides a structure for the reduction. Organising pharmacy dispensing at frequent intervals, such as once- or twice-weekly, will help the patient comply with the tapering plan. It is important to support the patient in this by not providing them with extra prescriptions without a review if they run out of medication before the scheduled time. At the review, reasons for the extra use should be explored, and the frequency of dispensing might be increased. In this way, patients would have fewer tablets available to them and, if they did take more than prescribed, they would not experience major withdrawal by the time of the next scheduled dispensing.

Taper rate and duration

A 10% reduction of daily dose of any opioid every one to two weeks is usually well tolerated, with no significant withdrawal. When one-third of the initial daily dose is reached, slow the tapering to half the previous rate to minimise withdrawal-related anxiety.[7]

The pace of the taper depends on the patient and the reason for tapering. If the patient is experiencing serious opioid-related side effects, a faster taper is necessary. An even more rapid tapering might be warranted if the patient is refusing to see an addiction

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specialist after exhibiting aberrant behaviour, such as injecting, or breaching the treatment agreement by obtaining medications from multiple sources. A slower rate of tapering is advisable for patients who are highly anxious about the process and who might have psychological dependence on the pain medications, or for those who have significant cardiorespiratory conditions.[7]

For patients who experience severe withdrawal symptoms or a worsening of function because of an increase in their pain levels or deterioration of their mood, it is best to hold the daily dose or increase it to a level at which they are comfortable. Slowing down the taper or lessening the amount of dose reduction at each taper might help in this scenario. Clinical reviews before each dose reduction ensure safety and help reduce anxiety. If the patient is adherent with the treatment agreement but cannot complete the taper, maintaining a lower dose with the same treatment structure may be an option.

It is advisable to suggest the option of substitution (also called 'maintenance') treatment as soon as failure to taper opioids or heavy reliance on opioid analgesia is observed.[8] As regulation and legislation regarding substitution treatment are governed by the states and territories in Australia, it is best to discuss the practicalities of this with a local addiction specialist or treatment centre.

The duration of the taper would depend on the initial dose and the patient's condition and adherence with the plan. It is advisable to include the intended taper duration in the initial treatment agreement and revise it if the plan changes.

Monitoring

Scheduling frequent visits for the patient, in keeping with the tapering rate and, if possible, before each dose reduction (e.g. weekly or fortnightly), will allow the prescribing doctor to monitor the patient's pain status, withdrawal symptoms and benefits of the taper, such as reduced pain and improved mood, energy level and alertness. These consultations should focus on the benefits of the taper, rather than simply the medication dose and rate. Using a urine drug screen to assess adherence for every patient who has been taking opioid analgesia for more than three months has now been accepted as good practice.[9] Medicare covers 36 urine drug screens within a period of 12 months if they are used for monitoring purposes. It is important to ask for testing of the exact agent used in the taper, as most pathology services do not routinely test for synthetic opioids such as oxycodone. The expectation is that the urine will test positive for the prescribed drug and negative for other opioids.

Involving allied healthcare professionals, especially a psychologist, during the taper is likely to increase the patient's capacity to deal with the negative thoughts and stress associated with the change in treatment. Excessive reliance or dependence on medication is often a stigmatised disorder to which patients cannot easily admit. It can be helpful to listen with empathy and without passing judgement, to acknowledge the patient's difficulty in controlling the medication use and to encourage their efforts.

Finally, it is essential to clearly explain to the patient, and document in the patient record, that alongside the reducing dose of opioids, the patient's tolerance for opioids will be altered as well. If the patient returns to taking the initial dose after a period of reduction, this reduced tolerance makes it likely that they may experience serious adverse effects, including opioid overdose and respiratory depression.

Conclusion

There are valid reasons to wean patients off their long-term use of opioid analgesics. A structured and well-planned tapering program will improve treatment outcomes and reduce the complications associated with opioid withdrawal. MT

3. WEANING OFF OPIOID THERAPY: USEFUL RESOURCES

Professional resources

- Opioid Tapering Calculator (Victoria State Government and NPS MedicineWise)
  - www2.health.vic.gov.au/Api/downloadmedia/%7B91501663-EA0B-4985-B996-74C159487EE3%7D
- Opioid Calculator App (FPM; ANZCA)
  - http://fpm.anzca.edu.au/front-page-news/free-opioid-calculator-app
- *A Guide to Deprescribing Opioids* (Tenni P, Orlikowski C; Deprescribing Clinical Reference Group; Primary Health Tasmania; 2016)
  - www.primaryhealthtas.com.au/sites/default/files/A%20Guide%20to%20Deprescribing%20Opioids.pdf
- *Recommendations Regarding the Use of Opioid Analgesics in Patients with Chronic Non-Cancer Pain* (FPM; ANZCA; 2015)
  - http://fpm.anzca.edu.au/Documents/PM1-2010.pdf
- *Quick Reference Recommendations for Conduct of an Opioid Trial in Chronic Non-Cancer Pain* (FPM; ANZCA; 2015)
  - http://fpm.anzca.edu.au/Documents/4462_001.pdf

Patient resource

- *Pain and Role of Medications* (Pain Management Network [Agency for Clinical Information])
  - www.aci.health.nsw.gov.au/chronic-pain/for-everyone/pain-and-role-of-medications

Abbreviations: ANZCA = Australian and New Zealand College of Anaesthetists; FPM = Faculty of Pain Medicine.

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Opioid prescribing in general practice

A proposed approach

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GPs can prescribe opioids optimally in their practices by following the five principles of opioid prescribing, utilising the five tools for assessment of use and using the five criteria for evaluating outcomes of an opioid trial.

The shared predicament of the patient with chronic noncancer pain and the primary care physician, both grappling with management of this complex problem, were discussed in a previous article.[1] We acknowledged that applying the desired biopsychosocial framework for assessment requires skill and time, the latter being at a premium in general practice. It was not at all surprising, therefore, that in practice the management of such patients generally defaults to the use of analgesic drugs, frequently opioids. Accordingly, a set of principles were presented that could be applied for the more judicious use of opioids in this context.

In this article we translate the principles previously described into a practical approach to opioid prescribing for patients with chronic noncancer pain. This updated version is presented in the face of the current controversy regarding the role of opioids in the management of patients with chronic noncancer pain, recognising that there is weak evidence of effectiveness and that harms are not inconsiderable.[2] This article is morally neutral on this issue but practical and realistic in its intent.

The framework for the approach presented comprises the five principles previously offered, five tools that may assist assessment and five criteria for evaluating the outcome of the ongoing trial of opioid pharmacotherapy in patients with chronic pain (Box 1).

Step 1. Comprehensive ('sociopsychobiomedical') assessment

The experience of chronic pain has social, psychological and biomedical contributions, each of which needs to be assessed.

'Socio-' (what is happening in the person's world)

Assess not only the effects of pain on relationships – family, friends, work and leisure

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KEY POINTS

- The complex experience of chronic pain has biological, psychological and social contributions, each of which you need to assess.
- Drug therapy for patients with chronic noncancer pain is only part of a multifaceted, multidisciplinary, treatment approach. If drugs are needed to treat patients with chronic noncancer pain, ensure you also pay attention to psychological and social stresses.
- Appreciate that opioid pharmacotherapy for patients with chronic noncancer pain is always an ongoing trial of therapy.
- Be aware of the regulations regarding opioid prescribing in your jurisdiction and of the 'rules' regarding PBS-subsidised opioids.
- Document any opioid trial carefully and if it is not working start tapering the dose to zero. If you are not sure what to do, ask for advice from a colleague experienced in chronic pain, a pain specialist, an addiction medicine specialist or a psychiatrist.

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1. FRAMEWORK FOR A PRACTICAL APPROACH TO OPIOID PRESCRIBING IN CHRONIC NONCANCER PAIN

5 principles

- Comprehensive assessment
- Poor response to other therapies
- Agreement regarding opioid trial
- Conduct of opioid trial
- Responses to difficulty achieving or maintaining goals in an opioid trial

5 tools

- Brief Pain Inventory
- Opioid risk tool (or other instrument)
- Contact numbers for advice regarding prescribing regulations in the different Australian jurisdictions
- Opioid contract
- Chart of opioid 'equianalgesic' doses

5 criteria

- Analgesia
- Activity
- Adverse effects
- Affect
- Aberrant behaviours

2. PROBLEMATIC OR ABERRANT DRUG-TAKING BEHAVIOURS

- Overwhelming focus on opioid issues, impeding progress with other issues
- Resistance to change in therapy despite evidence of adverse drug effects
- Aggressive complaining about the need for more drugs
- Noncompliance with use instructions, including nonsanctioned dosage escalation
- Pattern of prescription problems (i.e. lost, spilled or stolen medications)
- Supplemental opioids (from other providers, emergency departments or illicit sources)
- Stealing or 'borrowing' drugs
- Selling prescription drugs
- Prescription forgery
- Evidence of deterioration in function including family, work and social life
- Concurrent abuse of alcohol or other illicit drugs
- Injecting oral formulations

– but also the influence of other life events, ranging from changes within families to environmental disasters.

A useful tool to aid this assessment is the Brief Pain Inventory (see Toolbox 1). It allows patients to rate their pain on a scale of 0 to 10, where 0 is no pain and 10 is the worst pain possible.

An important part of this step is to assess the risk of problematic opioid use, by asking the following questions:

- Is there a personal or family history of past or current alcohol or drug problems?
- Is an active or recent psychiatric disorder present?
- Is there evidence of problematic drug-taking behaviours? (Box 2)

'Positive' responses here do not necessarily preclude a trial of opioid therapy but rather act as an alert to guide monitoring of a trial. A useful tool is the opioid risk tool (see Toolbox 2).[3]

'-psycho-' (what is happening to the person)

Assess the impact of pain on the patient's daily activities (work and recreation) and sleep. Explore the role of fatigue in the patient's condition. Chronic pain is often associated with changes in mood, especially depression and anxiety, and with loss of self-esteem. Much pain-related behaviour stems from patients' beliefs regarding diagnosis and prognosis that are frequently catastrophic and incorrect. Much distress can be alleviated by careful, accurate and realistic explanations, often about what is not wrong.

'-biomedical' (what is happening to the body)

Try to identify an underlying treatable condition, if suspected on the basis of clinical 'red-flag' features (e.g. inflammation, infection, neural pathology, neoplasm). However, most chronic pain is not due to a 'broken part' but is more likely to reflect altered function (in particular altered central nociception). This is especially so for pain experienced in musculoskeletal tissues. Finding the correct diagnostic language to use is difficult here. For example, 'lumbar spondylosis' is a statement of age-related anatomical fact and does not imply either the presence or mechanism of pain.

Step 2. Adequate trial of other reasonable therapies

Drug therapy – for symptom control – is an adjunct to a comprehensive care plan. Often that plan will need to include the help of other health professionals.

Nondrug treatment options include an accurate explanation, especially realistic prognostication (there is often no 'cure' for chronic pain) and advice regarding nutrition, exercise, sleep hygiene and the pursuit of pleasurable activities. Emphasise the need for daily activity, not rest, and the important role of pacing to limit fatigue. Consider referral of the patient to appropriate healthcare personnel, if available, for more intensive exploration of these options.

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TOOLBOX 1. BRIEF PAIN INVENTORY*

NAME: _____

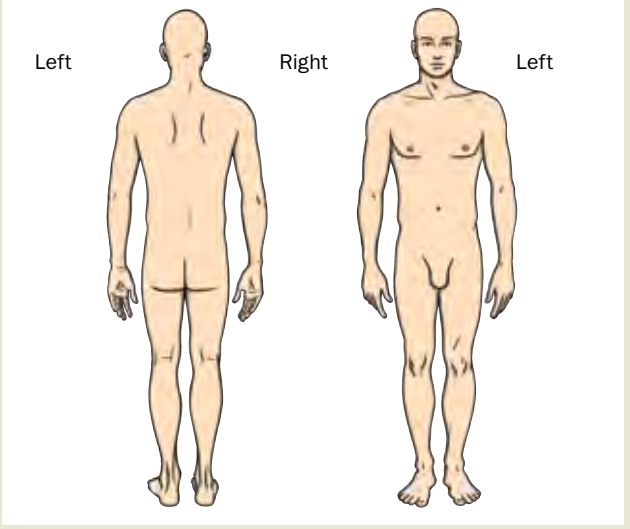
DATE: _____

TIME: _____

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes **2. No**

2. On the diagram, shade in the area where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No pain **Pain as bad as you can imagine**

4. Please rate your pain by circling the one number that best describes your pain at its least in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No pain **Pain as bad as you can imagine**

5. Please rate your pain by circling the one number that best describes your pain on average.

0 1 2 3 4 5 6 7 8 9 10

No pain **Pain as bad as you can imagine**

* Reproduced with permission from Dr Charles S. Cleeland (1991).

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10

No pain **Pain as bad as you can imagine**

7. What treatments or medications are you receiving for your pain?

_____

_____

8. In the past 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 10%

No relief **Complete relief**

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere **Completely interferes**

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere **Completely interferes**

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10

Does not interfere **Completely interferes**

D. Normal work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

Does not interfere **Completely interferes**

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not interfere **Completely interferes**

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

Does not interfere **Completely interferes**

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere **Completely interferes**

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As symptom control is important, consider the role of nonopioid analgesic medications, especially paracetamol. So-called adjuvant analgesics include tricyclic antidepressants, such as amitriptyline and nortriptyline (both used off label), serotonin and noradrenaline reuptake inhibitors, such as duloxetine and venlafaxine (both used off label), and anticonvulsants, such as gabapentin and pregabalin (both indicated for the treatment of neuropathic pain). These analgesics may have a role but may be limited by cognitive side effects, drowsiness or, in some cases, high cost.

In this context, invasive therapies, ranging from injections to implants, may not be considered 'reasonable', especially when there is no local 'broken part' to be fixed. Opioid use should be considered before invasive options.

Step 3. Agreement regarding opioid trial

Opioid pharmacotherapy for patients with chronic pain is an ongoing trial, repeatedly addressing the question, 'Is this patient's predicament opioid-responsive?'

Such a trial is always a part of a multimodal treatment plan. Given that opioids are controlled drugs, a 'contract' between prescriber and patient should be explicit, with ongoing prescription depending on evidence of worthwhile ongoing benefit and minimal harm. The agreement extends to:

- identifying realistic activity goals, tailored to the individual patient, that emphasise improved function, not just less discomfort
- one prescriber (and deputy) and a single pharmacy dispensing according to risk assessment, with no early repeat prescriptions or loss replacements
- setting review intervals, perhaps weekly for the initial trial and up to third-monthly for stable patients
- tapering dose to termination of the opioid trial if treatment goals

TOOLBOX 2. OPIOID RISK TOOL*[2]

Risk factor	Male (score)	Female (score)
Family history (parents and siblings)		
• Alcohol abuse	☐ (3)	☐ (1)
• Illegal drug use	☐ (3)	☐ (2)
• Prescription drug abuse	☐ (4)	☐ (4)
Personal history		
• Alcohol abuse	☐ (3)	☐ (3)
• Illegal drug use	☐ (4)	☐ (4)
• Prescription drug abuse	☐ (5)	☐ (5)
Mental health		
• Diagnosis of ADD, OCD, bipolar disorder or schizophrenia	☐ (2)	☐ (2)
• Diagnosis of depression	☐ (1)	☐ (1)
Other		
• Age 16 to 45 years	☐ (1)	☐ (1)
• History of preadolescent sexual abuse	☐ (0)	☐ (3)
Total score	_____	_____

Total score risk category:
0 to 3 = Low risk: 6% chance of developing problematic behaviours.
4 to 7 = Moderate risk: 28% chance of developing problematic behaviours.
≥8 = High risk: more than 90% chance of developing problematic behaviours.

Abbreviations: ADD = attention deficit disorder; OCD = obsessive compulsive disorder.

*Adapted with permission from Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. Pain Med 2005; 6: 432-442.

TOOLBOX 3. CONTACT NUMBERS FOR ADVICE REGARDING OPIOID

Jurisdiction	Agency	Telephone	Fax
ACT	Pharmaceutical Services, ACT Health	02 6205 0998	02 6205 0997
NSW	Pharmaceutical Services Branch, NSW Ministry of Health	02 9879 5239	02 9859 5175
NT	Poisons Control, Department of Health and Community Services	08 8922 7341	08 8922 7200
QLD	Drugs of Dependence Unit, Queensland Health	07 3328 9890	07 3328 9821
SA	Drugs of Dependence Unit, Pharmaceutical Services, SA Health	08 8274 3434	08 8274 3433
TAS	Pharmaceutical Services Branch, Department of Health and Human Services	03 6233 2064	03 6233 3904
VIC	Drugs and Poisons Regulation, Department of Health	1300 364 545	1300 360 830
WA	Pharmaceutical Services, Department of Health	08 9222 4424	08 9222 2463

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TOOLBOX 4. EXAMPLE OF A TREATMENT CONTRACT FOR THE USE OF OPIOIDS FOR THE MANAGEMENT OF CHRONIC PAIN*

Patient name: _____

Address: _____

Date of birth: _____

I, [Add name here], understand that opioid painkillers are being prescribed to me in an attempt to improve my level of functioning and reduce my pain intensity. My medical practitioner and I agree to the following conditions regarding my treatment and the prescribing of opioid medications for my pain. We have discussed that strong opioid (morphine-like) painkillers may be only partially helpful in achieving this goal and on occasion will not help at all. I understand that painkillers are only one part of the management of my chronic pain.

1. My medical practitioner is responsible for prescribing a safe and effective dose of opioids. I will not use opioids other than at the dose prescribed and I will discuss any changes in my dose with my medical practitioner.
2. I am responsible for the security of my opioid medicine. Lost, misplaced or stolen prescriptions or medicine will not be replaced.
3. I will only obtain opioid medications from the medical practitioner who signs this contract, or other doctors in the same practice authorised to prescribe to me. I understand that no early prescriptions will be provided.
4. Although most people do not have any serious problems with this type of medicine when used as directed, there can be side effects. My medical practitioner will let me know what these are and I will tell him or her if I experience them.
5. I am aware that my medical practitioner is required to gain authorisation from the Department of Health for continued prescription of these medications.
6. I agree to tell my medical practitioner if I have ever been dependant on alcohol or drugs, or if I have ever been involved in illegal activity related to any drugs including prescription medicines. I am aware that providing my medicine to other people is illegal and could be dangerous to them.
7. My medical practitioner respects my right to participate in decisions about my pain management and will explain the risks, benefits and side effects of any treatment.
8. My medical practitioner and I will work together to improve my level of functioning and reduce my pain.
9. I understand that my medical practitioner may stop prescribing opioids or change the treatment plan if my level of activity has not improved or I do not show a significant reduction in pain intensity, or if I fail to comply with any of the conditions listed above.

Patient signature: _____

Name: _____

Date: _____

Medical practitioner: _____

Provider number: _____

Date: _____

* Adapted from the Drug and Alcohol Office/Pharmaceutical Services Branch, WA Department of Health.

(including review appointments) are not met, there are serious adverse outcomes or there is evidence of misuse, especially unsanctioned use such as self-injection, stockpiling, selling or giving drugs to others
- including an option for random drug monitoring, such as by urine drug screen or pill counts.

Prescribers should be familiar with the regulatory requirements in the state or territory jurisdiction of their practice (see Toolbox 3 for contact numbers for Pharmaceutical Services Branches in each jurisdiction in Australia). Some jurisdictions may require an opioid contract to be signed by the patient and medical practitioner (see Toolbox 4). All prescribers should note the importance of attention to documentation, regulation and adherence to advice from the Pharmaceutical Services Branch in their jurisdiction of practice.

Step 4. Conduct of an opioid trial

A trial of opioid analgesic therapy requires goal-setting, explicit agreements, skilled titration of dose and regular monitoring of the 5A criteria.

The pharmacological principle of an opioid trial is to use long-acting (long half-life) oral or transdermal opioid preparations, dosing according to age (see Table). The starting dose should be low if the patient is opioid naïve, of the order of 10 mg daily oral morphine equivalent. If the patient is already taking an immediate-release opioid (e.g. codeine, morphine or oxycodone) or tramadol, calculate the daily dose and use the equianalgesic chart (see Toolbox 5) to convert it to an approximate daily equivalent of a long-acting oral or transdermal preparation.

Regularly reassess the patient and document details, according to the 5A criteria, which are:
- analgesia
- activity
- adverse effects
- affect
- aberrant behaviour.

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TABLE. SUSTAINED-RELEASE OR LONG-ACTING OPIOID PREPARATIONS FOR USE IN PATIENTS WITH CHRONIC NONCANCER PAIN

Generic name	Seek advice if dose exceeds
Oral opioid agonists	
Hydromorphone	12 mg daily
Methadone	20 mg daily
Morphine	60 mg daily
Oxycodone	40 mg daily
Oral opioid-like activity	
Tapentadol	150 mg daily
Tramadol	300 mg daily
Transdermal opioids	
Buprenorphine	30 mcg/h weekly
Fentanyl	25 mcg/h every three days

TOOLBOX 5. APPROXIMATE OPIOID DOSES EQUIANALGESIC TO ORAL MORPHINE 30 MG

Oral
- Tapentadol 75 mg
- Tramadol 150 mg
- Codeine 180 mg
- Dextropropoxyphene 130 mg
- Methadone 10 mg*
- Oxycodone 20 mg
- Hydromorphone 4 mg

Sublingual
- Buprenorphine 0.4 mg

Parenteral
- Tramadol 100 mg
- Morphine 10 mg
- Hydromorphone 1.5 mg

Transdermal
- Buprenorphine 20 mcg/h
- Fentanyl about 12 mcg/h

* Morphine:methadone 3:1 for morphine less than 100 mg daily only.

Whether initiating or continuing therapy, review weekly initially, then according to achievement of goals. Titration of dose according to the 5A assessment over four to six weeks should allow the fundamental question, 'Is this person's predicament opioid-responsive?', to be answered. A decision can then be made to continue maintenance therapy, subject to ongoing satisfactory assessments of the 5As, test the effects of dose reduction or taper to withdrawal.

The main focus of the opioid trial should be on improved function – physical, cognitive and social. How active does the patient want to be? Is the patient able to achieve this level of activity? Is that level of activity appropriate under the circumstances? Given the variable course of chronic pain, it may well be that over time opioid requirements fluctuate, not necessarily upward.

Try to tailor the drug regimen to individual patient needs, such as taking the drug at night only to ameliorate sleep, or asymmetrically varying the dose during the day according to required or anticipated activity levels. Limit the dose to a maximum of 100 mg daily oral morphine equivalent (see Toolbox 5). It is suggested that an apparent opioid requirement approaching this should trigger a comprehensive reassessment of the patient. If tapering of opioid therapy is required, the suggested rate is to reduce the daily dose by 10% each week.

If in doubt about any aspect of the opioid trial, enlist the opinion of a colleague or a specialist pain or addiction medicine physician. For regulatory purposes, this should be done at least annually in any case.

Step 5. Response to difficulty achieving or maintaining goals in an opioid trial, including demands for an increase in dose

Difficulty achieving or maintaining the goals of an opioid trial should trigger comprehensive reassessment of the patient (steps 1 to 4), which may then require referral.

The two main problems that may be encountered in an opioid trial are:
- a claim that there has been no change in pain despite evidence of increased function
- evidence of unsanctioned use of the drug.

However, the same principles apply, starting with repeat assessment, especially at the 'social-' and '-psycho-' levels of the framework. In patients with established chronic pain, it is unlikely that there will be a change in the underlying disease state, although alertness to clinical features suggesting such change is important. It is more likely that difficulty in achieving the goals reflects a change in the patient's psychosocial situation or a response to other life stressors.

In this situation, a new 'contract' can be negotiated, perhaps with revised goals and review plans, provided that the fundamental question, 'Is this person's predicament opioid-responsive?', has a positive answer. If there is evidence of increased function, it is probable that the trial is positive but the patient needs to observe better 'pacing' of activity. If relative under-dosage is suspected, a trial of increased dose can be considered, again to be evaluated using the 5A criteria. If adverse effects of the opioid are a problem but the trial is otherwise positive, changing to another opioid could be considered (see Toolbox 5). However, if there is evidence of unsanctioned opioid use (Box 2), taper the opioid to withdrawal

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and refer the patient to a specialist pain or addiction medicine physician.

What about the 'inherited' patient?

The 'inherited' patient, especially one taking more than 100 mg/day oral morphine equivalent, is a common situation. The same principles apply as for patients undergoing an opioid trial, namely:

- perform a sociopsychobiomedical reassessment (over time)
- establish new contract with set goals
- carry out regular 5A criteria assessment
- refer patient if in doubt.

When conducting an opioid trial in these patients:

- convert, in stages, all current opioids that the patient is taking to one form only of nonparenteral opioid. (Transdermal fentanyl is not recommended as rapid tolerance appears to be a problem and dose titration is difficult.) For example, 80% current opioids and 20% new opioid for a week, then 60% current opioids and 40% new opioid for a similar period, then 40% current opioids and 60% new opioid, etc to full conversion
- the patient may find that the current preferred opioid has high 'likeability'. In that case, conversion may take several months. Be prepared to slightly increase the dose of the new main opioid
- seek to establish the lowest dose of the one opioid species that facilitates the patient maintaining activity in reasonable comfort with minimal side effects. Each decrement could be 10% of the current daily dose. It may not matter if the opioid cannot be withdrawn completely, provided that the patient is able to be as active as he or she wishes to be
- involve the patient in decision making about the transition unless it becomes clear that the patient is sabotaging that process. In that case, the patient should be referred to a specialist.

Pain management in the opioid-dependent ('addicted') patient

Many people on opioid-substitution treatment programs (with methadone or buprenorphine) have concurrent chronic pain. This is likely to be as difficult to treat as in other patients and only partly responsive to opioid treatment.

The request for an increased opioid dose to reduce the severity of pain can be considered on a trial basis but any change to a 'preferred' drug should be resisted. If possible try to manage chronic pain in patients on opioid-substitution treatment by increasing the dose of methadone or buprenorphine rather than by introducing another opioid.

Otherwise consider referring the patient for specialist advice. An exception might be presentation with an episode of acute nociception, such as bony trauma, in which case a temporary increase in dosage of the current opioid could be considered.

Conclusion

The cornerstones of quality use of opioids in the management of patients with chronic noncancer pain are:

- comprehensive sociopsychobiomedical assessment
- ongoing trial of opioid responsiveness using long-acting oral or transdermal preparations
- regular 5A re-evaluation
- careful documentation of goals, decisions and advice received. MT

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