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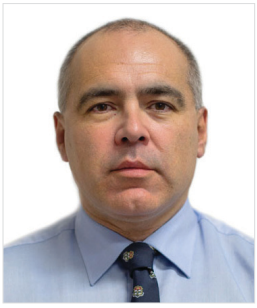
Non-opioid Analgesics and Non-traditional Opioids in General Practice



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This article discusses the use of non-opioid analgesics and non-traditional opioids in the management of pain in General Practice

Introduction

In this article, the term 'traditional opioids' refers to drugs that have activation solely of the mu-opioid receptor as their mechanism of action. 'Non-traditional opioids' refers to those drugs that have agonist/antagonist effects at the mu-opioid receptor, or have activation of other receptors as well, such as serotonin and noradrenaline. Medications predominantly used for neuropathic pain will not be reviewed here as these warrant an article in their own right. This article will focus on options for nociceptive pain outside pure mu-opioid analgesics.

Prior to the seminal paper 'Chronic use of opioid analgesics in non-malignant pain: report of 38 cases' by Portenoy and Foley, published in 'Pain' in 1986,[1] there was limited use of opioids in chronic non-cancer pain. Opioid use was predominantly limited to buprenorphine, and small amounts of methadone and levorphanol were used at low dosages. These three medications were used in preference to pure mu-opioids because of the reduced tolerance and dependence

Take Home Messages

- There is a limited evidence base for the use of paracetamol in chronic non-cancer pain.
- Before prescribing NSAIDs, ensure the patient has no contraindications (cardiac disease; asthma, prescribed anticoagulation; renal or liver impairment; a past history of gastric or duodenal ulceration).
- Tramadol is particularly effective in treating neuropathic pain and this is supported by a Cochrane systematic review.
- Tapentadol is efficacious in treating neuropathic, nociceptive and inflammatory pain types, with demonstrated efficacy in both cancer pain and chronic non-cancer pain conditions (such as osteoarthritis and low back pain).

associated with them. Portenoy and Foley's publication changed prescribing and ushered in the extensive use of pure mu-opioids for the treatment of chronic non-cancer pain. Issues of tolerance, dependence, medication misuse and abuse, overdose, opioid-induced hyperalgesia, neurological effects, increased mortality and other adverse effects, however, have subsequently led to the realisation that pure mu-opioids have a limited role to play in chronic non-cancer pain.[2-5] Furthermore, extensive and current reviews of opioid efficacy for chronic non-cancer pain have reported limited success in terms of analgesia (approximately 30% of chronic non-cancer pain patients report success), and poor evidence for long-term efficacy of opioids.[2, 6, 7] This has led to a renewed interest in non-opioids and non-traditional opioids in the management of chronic non-cancer pain.[8-10] This article will attempt to outline those options and how they can be appropriately prescribed.

Non-opioid Analgesics

Three typical non-opioid analgesics considered for chronic non-cancer pain are paracetamol, nonsteroidal anti-inflammatory agents and the muscle relaxant orphenadrine.

Paracetamol

Paracetamol is considered a first-line therapy for acute and chronic pain. It is typically taken as extended-release paracetamol, eight or twelve hourly. There is a limited evidence base for use of paracetamol in chronic non-cancer pain.[11-13] A recent Cochrane review has concluded that the majority of randomised controlled trials assessing its efficacy for acute low back pain are of low quality and that further, larger studies are warranted.[14,15] This should not, however, discount the relevant literature showing its efficacy in various chronic non-cancer pain conditions, such as pain due to musculoskeletal diseases, particularly those studies that have shown that strong opioids are no more effective than paracetamol.[16] This may support its use as an opioid sparing agent for chronic non-cancer pain.

Paracetamol is generally inexpensive, easily obtainable and safe. Reports do, however, indicate a small yet significant population of patients with chronic non-cancer pain who exceed the recommended daily dose limit. This group includes those who use paracetamol in conjunction with opioids to augment analgesia. Health professionals should be proactive in identifying and managing patients at risk of adverse effects from such behaviours.[17-19]

Non-steroidal Anti-inflammatory Agents

Non-steroidal anti-inflammatory drugs (NSAIDs) are most likely to have a positive effect in inflammatory and nociceptive pain conditions by blocking prostaglandin synthesis via cyclooxygenase (COX) inhibition.[8, 20] They are used as slow-release preparations

for longer lasting pain and also as short-acting treatments for breakthrough pain relief. NSAIDs have shown limited efficacy in chronic, non-cancer pain and there is a recent Cochrane systematic review outlining this topic.[21] There is, however, some evidence of efficacy in chronic low back pain.[22-24] Typically, up to three NSAIDs should be trialled before the patient can be declared unresponsive to this treatment for their persistent pain (the personal opinion of the author).

Before advising the use of NSAIDs, it should be noted that the patient should not have comorbidities that place them at high risk of complications (such as cardiac disease; asthma; prescribed anticoagulation; renal or liver impairment; a past history of gastric or duodenal ulceration).[23] Consideration should also be given to the fact that there are idiosyncratic responses (hypersensitivities) to NSAIDs.[25] As COX-1 inhibition is associated with a higher occurrence of adverse effects, especially respiratory, NSAIDs that selectively inhibit COX-2 (coxibs such as celecoxib) have demonstrated improved tolerability and are safe to use in patients with certain NSAID intolerances, for example, asthma.[20]

Orphenadrine

Orphenadrine is a muscle relaxant. It is primarily an anticholinergic agent, with mild antihistaminergic properties and it interacts with a wide variety of neurotransmitters and other receptors. Its analgesic mechanism of action is relatively unknown.[26] It appears to have a particular role for treating the pain due to muscle hypertonicity or muscle spasm. It is typically commenced at a dose of 50mg twelve hourly, with a maximum dose being regarded as 100mg twelve hourly. Orphenadrine is generally contraindicated in patients with glaucoma and urinary retention.[17] The author's suggestion is that orphenadrine is particularly useful in pain states associated with early morning stiffness lasting more than twenty minutes. Orphenadrine is synergistic in its analgesia when combined with paracetamol.[27]

Nutraceuticals in the Management of Osteoarthritis Pain

There is an evolving interest in the use of nutraceuticals for the management of osteoarthritis pain because of the apparent absence or minimal occurrence of side-effects compared to more typical prescribed agents, such as the NSAIDs.[28] Many nutraceuticals have claimed to have a role re symptom relief in osteoarthritis. There is evolving evidence for green-lipped mussel extract,[29, 30] glucosamine/chondroitin combination,[31, 32] omega-3 fish oil[33] and curcumin.[34-36] Whether these agents are optimally used individually or in combination has not been well researched, although one trial has reported enhanced efficacy with a combination of glucosamine and omega-3 fish oils.[37] Clinical experience shows that there are patient subgroups that are more likely to respond to certain nutraceuticals, but that this cannot be predicted in advance. Typically in clinical practice, 1 to 4g daily of omega-3 fish oil (as recommended[38]) is combined with empirical trials of green-lipped mussel extract, glucosamine/chondroitin and curcumin, sequentially.

Non-traditional Opioids

The term 'non-traditional opioids' is best applied to those opioids that are not pure, or full, mu-agonists (such as buprenorphine, tramadol and tapentadol). Additional non-traditional opioids such as levorphanol are available overseas. Like the traditional opioids, investigations into the efficacy of these agents in chronic non-cancer pain conditions offer somewhat mixed results. Importantly, however, they have been shown to have significantly reduced rates of tolerance, dependence, addiction and opioid-induced hyperalgesia. There is evidence of reduced accidental fatal overdose, and so all of these factors make them a much safer and favourable analgesic option. These agents will be discussed in brief and the readers are referred to more extensive reviews on these drugs individually.[39-43]

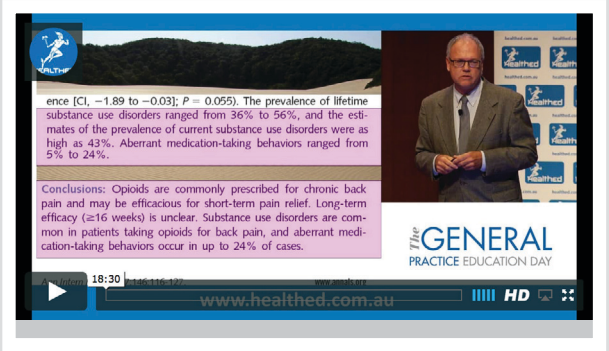
Buprenorphine

Buprenorphine is a mixed opioid receptor agonist/antagonist. It has partial agonism at the mu-opioid receptor and antagonism at the kappa- and delta-opioid receptors, and it is through this mechanism that buprenorphine is thought to have reduced expression of pure mu-opioid type adverse effects (including psychotropic effects, and hence a lower risk of misuse).[44]

> Various studies and clinical trials have provided support for the analgesic efficacy and improved tolerability of transdermal buprenorphine in numerous conditions of chronic non-cancer pain, whether these are neuropathic, nociceptive or mixed pain types

Buprenorphine is available as both a sublingual (Temgesic®) and a transdermal preparation (Norspan®). The sublingual preparation is usually started at a dose of 0.2 to 0.6mg per day and titrated according to the patient's response (typically 0.6mg to 2mg per day). Its duration of action is typically about eight to twelve hours and it can be used on either a regular or breakthrough basis. The transdermal preparation is applied once every seven days. Various studies and clinical trials have provided support for the analgesic

Video Resources



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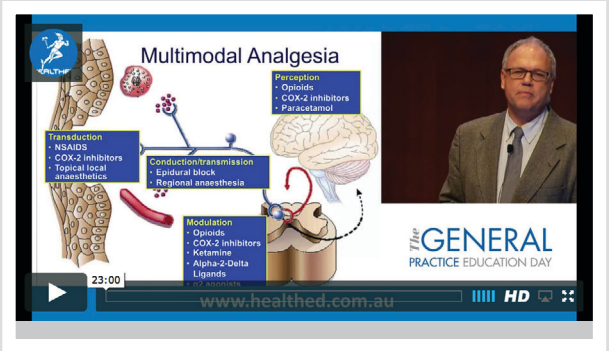
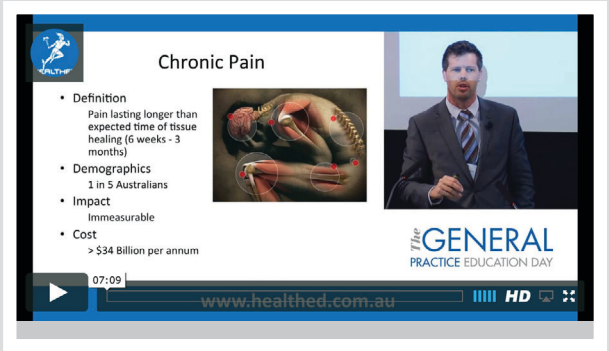


Optimising Management of Acute Pain in GP by Prof Stephan Schug



Safer and More Effective Use of Opioids in Chronic Pain by Dr Richard Sullivan

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efficacy and improved tolerability of transdermal buprenorphine in numerous conditions of chronic non-cancer pain, whether these are neuropathic, nociceptive or mixed pain types (including osteoarthritis, low back pain, post-herpetic neuralgia and diabetic neuropathy).[42, 45]

Buprenorphine is associated with various opioid-like side-effects, such as nausea, vomiting, constipation and pruritus. However, unlike full mu-opioid agonists, buprenorphine appears to have a ceiling effect on respiratory depression to a point of decreasing minute ventilation by 50%, thus limiting the occurrence of overdose and potential fatal adverse events.[45] Due to its slow and reversible agonism of the mu-opioid receptor, buprenorphine is also often used as a substitute drug in cases of opioid dependence to reduce withdrawal symptoms, cravings and relapse.[46]

Tramadol

Tramadol is a weak mu-opioid agonist consisting of two enantiomers which together also inhibit noradrenaline and serotonin reuptake. These mechanisms synergistically increase the amount of descending inhibition at the level of the brain stem to augment the weak opioid receptor agonistic effects and produce a clinically effective analgesic.[40,41,47,48] Tramadol is available in immediate release, slow release and extended release oral preparations, and the maximum dose is 400mg daily. It is particularly effective in treating neuropathic pain and this is supported by a Cochrane systematic review.[40] Another Cochrane review concluded that it has a small, but positive effect on pain, symptoms and functionality in osteoarthritis patients.[39]

> Tramadol may be associated with seizures and hence should be avoided or used cautiously in patients with epilepsy

Side-effects are generally mild and reversible and the most common are gastrointestinal (namely nausea, vomiting and constipation) and central nervous system effects (namely dizziness, headache and somnolence).[49] It is thought that the reduced severity of these opioid-related side-effects is due to partially opposing effects of the two enantiomers.[50] Tramadol may be associated with seizures and hence should be avoided or used cautiously in patients with epilepsy. Caution should also be exercised when using high doses

of tramadol in conjunction with high-dose psychotropic medications that act through serotonergic pathways, as serotonin syndrome has been reported, albeit rarely. There is very limited evidence that tramadol alone can produce serotonin syndrome.[51] Doses should be adjusted in elderly patients and in patients with hepatic or renal insufficiency.[52]

Tapentadol

Tapentadol is a newer 'atypical' opioid analgesic that is available in both extended release and now immediate release formulations, although the latter format is not listed on the Pharmaceutical Benefits Scheme. The recommended initial dose is 50 to 100mg every twelve hours, with a typically established daily dose within the range of 50 to 500mg. Tapentadol is somewhat structurally similar to tramadol, with lower affinity for mu-opioid receptors than traditional opioids, and with additional noradrenaline reuptake inhibition activity that augments suppression of pain signals in the spinal cord/brain stem.[53] Unlike tramadol, however, tapentadol has negligible activity at the serotonin receptor and should therefore have no interaction with serotonergic medications in terms of an ability to produce serotonin syndrome. It is also a more potent mu-opioid receptor agonist than tramadol, has a single enantiomer and does not have an active metabolite, thus it has significantly different pharmacodynamic and pharmacokinetic properties.[54]

Tapentadol has been shown to be efficacious in treating neuropathic, nociceptive and inflammatory pain types, and has demonstrated efficacy in both cancer pain and chronic non-cancer pain conditions (such as osteoarthritis and low back pain).[55,56] Numerous studies have compared tapentadol to oxycodone, with studies showing equi-analgesic efficacy, but a reduced incidence or severity of side-effects with tapentadol, as well as a lower discontinuation rate and a lower incidence of withdrawal symptoms.[56] In a more recent meta-analysis of tapentadol efficacy in chronic non-cancer pain, 25% of patients prescribed tapentadol were found to have a superior analgesic response compared to tramadol, 50% were found to have equi-analgesic response, and 25% were found to have a poor response, or were unable to tolerate the medication due to side-effects.[41] A Cochrane review of the use of tapentadol for chronic musculoskeletal pain concluded that there were small, yet positive benefits with tapentadol treatment, and that it was more effective and tolerable than oxycodone.[43]

Tapentadol has a similar yet less severe side-effect profile compared to traditional opioids, particularly in terms of its gastrointestinal and central nervous system effects, and is hence better tolerated and less likely to be discontinued. The most common side-effects include nausea, vomiting, dizziness, somnolence, headache and pruritus.[53] As tapentadol does not have an active metabolite, it may be used in elderly patients and in those with moderate hepatic or renal insufficiency without dose adjustment.[56] Tapentadol is contraindicated in patients with severe respiratory disorders (especially significant respiratory depression, asthma and unmonitored hypercapnia), paralytic ileus, and in patients taking monoamine oxidase inhibitors, and it should be used with caution in patients at risk of seizures and in those taking other antidepressant medications or central nervous system depressants.[56] The available data shows that tapentadol has a low risk of medication abuse.[57]

Analgesic medications used as an alternative to traditional opioids

Non-opioid medications

- Paracetamol
- Non-steroidal anti-inflammatories
- Orphenadrine
- Complementary therapies currently under research
  - Green-lipped mussel extract
  - Glucosamine/chondroitin combination
  - Omega-3 fish oil
  - Curcumin

Non-traditional opioids

- Buprenorphine
- Tramadol
- Tapentadol

Conclusion

A return to pre-1986 prescribing practice for chronic non-cancer pain can be argued. The modern management of chronic non-cancer pain should initially focus on the use of non-opioid analgesics and non-traditional opioid analgesics, as these have significantly lower rates of tolerance, dependence, addiction and opioid-induced hyperalgesia and overall, more favourable side-effect profiles. Subsequently, rational use of low-dose, pure mu-opioids may be considered, adhering to recent Faculty of Pain Medicine Guidelines.[58]

Non-traditional opioids would now include buprenorphine, tramadol and tapentadol, whereas non-opioid options would include paracetamol, nonsteroidal anti-inflammatory agents and orphenadrine. Regarding symptomatic osteoarthritis, nutraceutical use is an evolving area. Although initially positive clinical effects have been demonstrated, more research is required to elucidate how best these substances can be used. Patients may choose to use these as a foundation of therapy to which prescription medication can be added, starting with non-opioids and, if required, progressing to the addition of non-traditional opioids.

Appropriate guidelines for prescribing should be considered, starting with a trial of the therapy using the lowest dose possible and assessing the outcome.[59] Criteria for ongoing prescription include a reduction in pain and improvement in functional capacity without worsening quality of life. The trial of an opioid would cease (as is usual for any of the pain medications), if analgesic response is lacking.

Declaration

Dr Marc Russo and Dr Willem Volschenk were commissioned by Healthed for this article. The ideas, opinions and information presented are solely those of the authors. The advertiser does not necessarily endorse or support the views expressed in this article. The authors' competing interests statements can be viewed at www.healthed.com.au/monographs.

Further Reading

Detailed guidelines for non-opioid treatment of chronic non-cancer pain and management of opioid use are available from the Institute of Clinical Systems Improvement (ISCI):

Hooten M, Thorson D, Bianco J, Bonte B, Clavel Jr A, Hora J, Johnson C, Kirksson E, Noonan MP, Reznikoff C, Schweim K, Wainio J, Walker N. *Institute for Clinical Systems Improvement.* Updated for Public Comment July 2016. Available online at: https://www.icsi.org/_asset/3chfl8/PainPC0716.pdf

CDC guideline for prescribing opioids for chronic pain – United States, 2016: Dowell D, Haegerich TM, Chou R. *JAMA.* April 2016; 315(15):1624-1645. Available online at: http://jamanetwork.com/journals/jama/fullarticle/2503508

Recommendations regarding the use of opioid analgesics in patients with chronic non-cancer pain: *Faculty of Pain Medicine. Australian and New Zealand College of Anaesthetists.* June 2015. Available online at: http://fpm.anzca.edu.au/documents/pm1-2010.pdf (http://fpm.anzca.edu.au/resources/professional-documents)

Expert advice against the prescription of opioid medications: Hayes C. *Chronic pain*. MedicineWise News. 2015 June. Available online at: http://www.nps.org.au/publications/health-professional/nps-news/2015/chronic-pain

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A list of references is included in the website version of this article. Go to www.healthed.com.au/monographs

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