

OPIOIDS (UPDATED AUGUST 2007)

CLINICAL QUESTION

Are opioids (oral or transdermal) safe and effective in the management of chronic non-malignant pain \geq 3 months' duration?

THE EVIDENCE

Treatment	Condition	Comparator	Relevant Results/Authors' Conclusions [#]
Long-acting opioids ^{†(1)} (administered orally or transdermally \leq twice/day)	Chronic non-malignant pain (> 6 months' duration)	Different types of long-acting opioids	Unable to determine whether one long-acting opioid is superior to another in terms of efficacy or safety (treatment period range 7 days to 6 weeks).
		Short-acting opioids (administered > three times/day)	Moderate evidence that long-acting oxycodone and short-acting oxycodone are equally effective for pain control (treatment period range 5 days to 16 weeks). Unable to determine whether long-acting opioids as a class are safer and more effective than short-acting opioids.
Weak opioids ^{‡(2)} (codeine, propoxyphene, tramadol) Strong opioids ^{‡(2)} (morphine, oxycodone) (administered orally for \geq 7 days)	Chronic non-malignant pain (> 6 months' duration)	Placebo	Strong evidence that opioids of any type reduce pain and improve function better than placebo in patients with nociceptive or neuropathic pain or fibromyalgia (treatment period range 1 to 13 weeks). Opioids were more likely to cause constipation, nausea, dizziness or vertigo, somnolence or drowsiness, vomiting, and dry skin, itching, or pruritus, than placebo.
		Non-steroidal anti-inflammatory drugs (NSAIDs) (acetaminophen, diclofenac, ibuprofen, naproxen, suprofen)	Strong evidence that weak opioids are less effective than NSAIDs in relieving pain and improving function (treatment period range 1 to 24 weeks). Limited evidence that strong opioids are superior to naproxen with respect to pain relief but not functional outcomes (over a 6-week treatment period). Opioids are more likely to cause constipation, nausea, and somnolence or drowsiness, but less likely to cause diarrhoea, than NSAIDs.
		Tricyclic antidepressants (TCAs) (clomipramine, levomepromazine, nortriptyline)	Limited evidence that weak opioids are less effective than TCAs in relieving pain and improving function (over a 6-week treatment period). Limited evidence that strong opioids are superior to nortriptyline with respect to pain relief but not functional outcomes (over a 6-week treatment period). Opioids are more likely to cause constipation, nausea, and somnolence or drowsiness, but less likely to cause diarrhoea, than TCAs.
Weak opioids ^{§¶(3)} (tramadol alone or combined with acetaminophen) (administered orally for \geq 1 month)	Chronic non-malignant, non-specific low back pain (> 3 months' duration)	Placebo	Moderate evidence that tramadol alone or combined with acetaminophen reduces pain and improves function better than placebo (treatment period range 30 to 90 days). Opioids are more likely to cause headache, nausea, somnolence, constipation, dry mouth, and dizziness than placebo.
Strong opioids ^{¶¶(3)} (daily set-dose oxycodone up to 30 mg morphine-equivalent or titrated dose oxycodone and morphine up to 200 mg morphine-equivalent) (administered orally for \geq 1 month)	Chronic non-malignant, non-specific low back pain (> 6 months' duration)	Naproxen	Limited evidence that oxycodone and naproxen are equally effective in relieving pain and improving function. Follow-up at 32 weeks. Oxycodone is more likely to cause dry mouth, drowsiness, headaches, constipation, and nausea than naproxen.

[†]Based on 16 **AVERAGE*** quality randomised controlled trials (RCTs), as assessed by the authors of this review, published between 1989 and 2002 and 8 observational studies (for adverse events only) published between 1995 and 2002; [‡]Based on 23 **GOOD***, 11 **AVERAGE***, and 5 **POOR*** quality RCTs published between 1983 and 2004; [§]Based on three **AVERAGE*** quality RCTs published between 2000 and 2004; [¶]Based on one **POOR*** quality RCT published in 1998; ^{¶¶}These studies are a subset from the Furlan et al. (2006) systematic review on chronic non-malignant pain above; [#]Refer to Grading Key document for explanation of evidence grading

ADDITIONAL NOTES

The opioids included in the RCTs are: codeine (Codeine Contin[®], Tylenol[®] #1,2,3,4); dextropropoxyphene and propoxyphene (Darvon-N[®]); dihydrocodeine; LA morphine (Kadian, MS Contin[®], MS.IR[®], M-Eslon[®], M.O.S.-Sulfate, ratio-Morphine SR, Statex[®]); oxycodone (OxyContin[®], Oxy-IR[®], Percocet[®], Percodan[®], Supeudol[®]); tramadol (Tramacet[®], Zytram XL); and transdermal fentanyl (Duragesic[®]). All of these drugs, except dihydrocodeine, are included in the Compendium of Pharmaceuticals and Specialties (2006).

IMPLICATIONS FOR PRACTICE

What we don't know:

- Is one opioid safer and more effective than another? Is one opioid safer and more effective than another in particular patient subgroups?
- Are long-acting opioids safer and more effective than short-acting opioids? How durable is the effect of opioid treatment?
- What is the minimum dose of opioids required to achieve a clinically significant treatment effect?
- Are opioids safer and more effective than non-opioid drugs other than non-steroidal anti-inflammatory drugs (NSAIDs)?
- Are the safety and effectiveness of opioids affected by the route of administration (e.g. oral versus rectal or infusion program)?
- How safe is long-term opioid therapy? What is the likelihood that a patient will develop opioid tolerance or addiction?

Research Evidence: What we know

In patients with chronic non-malignant pain, evidence indicates that:

- opioids reduce pain and improve function better than placebo over the short to medium term;
- long-acting oxycodone and short-acting oxycodone are equally effective for pain control;
- weak opioids (codeine, propoxyphene, tramadol) are less effective than NSAIDs or tricyclic antidepressants in relieving pain and improving function;
- strong opioids (morphine, oxycodone) are more effective than naproxen or nortriptyline in relieving pain.

In patients with chronic non-malignant, non-specific low back pain, evidence indicates that:

- tramadol, either alone or combined with acetaminophen, reduces pain and improves function better than placebo over the short to medium term;
- strong opioids (morphine, oxycodone) and naproxen are equally effective in relieving pain and improving function over the long term.

Recommendation from Clinical Ambassadors

Long-term use of weak opioids, like codeine, should only follow an unsuccessful trial of non-opioid analgesics; but in severe chronic pain, opioids are worth careful consideration. Patients frequently prefer long-acting opioids because they only have to take them once or twice a day.

Careful attention to incremental changes in pain intensity, function, and side effects is required to achieve optimal benefit. Because little is known about the long-term effects of opioid therapy, it should be monitored carefully; opioid side-effects should be high in the differential diagnosis of new complaints.

A history of addiction is a relative contraindication. Seek advice from a pain or addictions specialist, or a psychiatrist, before starting patients with a history of addiction on opioids.

The Clinical Ambassadors: Dr Saifee Rashiq, Dr Chris Spanswick, Dr Paul Taenzer

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References: This Evidence Brief is based on results from one **AVERAGE*** quality SR: ⁽¹⁾Chou et al. Comparative efficacy and safety of long-acting oral opioids for chronic Non-cancer pain: a systematic review. *Journal of Pain and Symptom Management* 2003;26(5):1026-48; two **GOOD*** quality systematic reviews (SR): ⁽²⁾Furlan et al. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ* 2006;174(11):1589-1594; ⁽³⁾Deshpande et al. Opioids for chronic low-back pain. *Cochrane Database of Systematic Reviews* 2007;(3):CD004959

***Quality ratings for RCTs & SR:** Good ● Average ● Poor ●

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