THERAPEUTICS

Opioids for chronic non-cancer pain

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic for this series, please email us at practice@bmj.com.

A 36 year old carpenter has a six month history of lower back pain with no specific clinical or radiological findings. As his pain has not responded to paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), he asks his doctor if he can have "stronger painkillers" such as morphine.

What are opioids?

Opioids are a group of compounds that act by binding to opioid receptors (μ, κ, and δ), which are widely distributed in the brain, spinal cord, and peripheral tissues. They are the mainstay in the management of cancer pain, but published data show a continual increase in the volume of prescribed opioids to manage moderate to severe, chronic, non-cancer pain.[1 2]

Changes in attitude and aggressive marketing have driven a dramatic increase in use, with more adverse events, including deaths from overdose (now the second leading cause of accidental death in the US).[3] Proponents claim that opioids are underused for chronic pain,[4] but lack of good scientific data has prevented the formulation of evidence based guidelines for their use, especially in primary care.

How well do opioids work in chronic non-cancer pain?

Several meta-analyses of the effectiveness of opioids have been published. Most of the randomised clinical trials summarised in these meta-analyses were funded by the pharmaceutical industry and report heterogeneous, short term outcomes in highly selected patients. Non-randomised and uncontrolled observational studies make up the rest of the literature. Nevertheless, most studies have consistently shown some effectiveness in chronic non-cancer pain by reducing pain intensity. In particular, meta-analyses show the efficacy of opioids in neuropathic pain,[5-7] although most guidelines regard opioids only as second or third line treatment for such pain because of their risk:benefit profile.[8 9] The data are even less encouraging for chronic non-neuropathic pain, the focus of this paper. A 2009 Cochrane review of 10 randomised or quasi-randomised controlled trials compared opioids (oral codeine, oxycodone, oxymorphone, morphine, and transdermal fentanyl) for chronic non-cancer pain (osteoarthritis of the knee or hip) with placebo or no treatment in 2268 participants.[10] The results (see table 1) led to the conclusion that small to moderate beneficial effects of non-tramadol opioids are outweighed by large increases in the risk of adverse events, and so they should not be routinely used even for severe osteoarthritic pain.

The assessment of long term efficacy is even more difficult, as randomised controlled outcome studies with a follow-up beyond six weeks are rare. A 2011 systematic review evaluated 21 randomised trials of opioids (transdermal fentanyl and buprenorphine, oral morphine, tramadol, oxycodone, oxymorphone, tapentadol, and hydromorphone) for chronic non-cancer pain with a minimum of 12 weeks of follow-up.[11] Trial quality was variable. Effectiveness of tramadol for osteoarthritis was borderline; for all other opioids and all other conditions, there was poor evidence of effectiveness.

A 2010 Cochrane review of long term opioid management for chronic non-cancer pain (at least six months of treatment) reviewed 26 studies with 4893 participants.[12] Quality of data was weak, with 25 case series or uncontrolled continuations of long term trials and only one randomised controlled trial. All three modes of administration were associated with clinically significant pain reduction. However, many participants stopped treatment because of adverse effects or insufficient pain relief. The authors concluded that the evidence for pain relief with long term opioid use was weak, while that for quality of life or functional improvement was inconclusive.

A cross sectional Danish study to evaluate the long term effects of opioids on pain relief, quality of life, and functional capacity for more than 16 000 people with chronic non-cancer pain showed that opioid treatment did not seem to fulfil any of the treatment goals. Although causative relationships could not be ascertained, opioid use was significantly associated with reporting of moderate, severe, or very severe pain, poor self rated health, being unemployed, higher use of the healthcare system, and a reduced quality of life.[13]

Table 1 | Results of a 2009 Cochrane review of 10 controlled trials that compared opioids (oral codeine, oxycodone, oxymorphone, morphine, and transdermal fentanyl) with placebo or no treatment for chronic non-cancer pain (osteoarthritis of the knee or hip) in 2268 participants[10]

Outcome parameter	Effect (95% CI)	Quality of evidence (based on GRADE)
Pain relief* (median)	NNT 8 (7 to 11)	High
Function*	NNT 10 (8 to 15)	High
All adverse events*	NNH 12 (10 to 16)	Moderate
Drop out due to adverse events*	NNH 19 (13 to 29)	High
Serious adverse events*	Little evidence of harmful effect (NNH not statistically significant)	Low
Withdrawal symptoms†	No evidence based assumption could be made for calculation of NNH	Low

*Median follow-up for 4 weeks. †Follow-up for 8 weeks.
NNT=number needed to treat (how many patients have to be treated in order to prevent one additional bad outcome (the higher the NNT, the less effective is the treatment)).
NNH=number needed to harm (how many patients have to be exposed to a risk factor over a specific period to cause harm in one patient that would not otherwise have been harmed (the lower the NNH, the worse the risk factor)).

How safe are opioids for treating chronic non-cancer pain?

Serious harms associated with opioids include

- Falls leading to fractures (opioid use in a group of patients with fractures 8.0% *v* 3.2% in a matched control group)[14]
- Respiratory depression—This can be fatal but is rare with long term treatment and occurs most commonly with dosing changes, errors, or misuse
- Deaths—Increasing use of opioids for chronic non-cancer pain is paralleled by rapidly rising numbers of deaths related to prescription opioids.[3 15] Causes include inappropriate intake by the patient, physician error in prescribing (in particular rapid escalation or introduction of high opioid doses in opioid-naive

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Previous articles in this series

- Carbapenem antibiotics for serious infections (*BMJ* 2012;344:e3236)
- Bisphosphonates in the treatment of osteoporosis (*BMJ* 2012;344:e3211)
- Maintenance drugs to treat opioid dependence (*BMJ* 2012;344:e2823)
- Cholinesterase inhibitors and memantine for symptomatic treatment of dementia (*BMJ* 2012;344:e2986)
- Antimuscarinic drugs to treat overactive bladder (*BMJ* 2012;344:e2130)

patients), and diversion of prescription opioids (estimated to occur in at least 4% of all opioid doses prescribed in the US[16]).

Other possible harms include

- Negative endocrine effects, mainly via the hypothalamic-pituitary-adrenal axis, leading to opioid induced androgen deficiency (OPIAD, reduced testosterone production leading to osteoporosis and immune suppression) in men, with recent data suggesting that up to five million men have OPIAD in the US[17]
- Opioid induced hyperalgesia (worsening pain sensitivity in patients chronically exposed to opioids) has been shown in experimental settings. Despite inconsistent clinical evidence, it may have important implications in the treatment of chronic pain, particularly with high opioid doses and in those with an underlying central sensitisation disorder (such as fibromyalgia)[18]
- Potential for abuse and opioid addiction—Data are inconsistent, often underestimating risk, and seem to depend on a wide range of factors: a Cochrane review of long term use reported signs of iatrogenic opioid addiction in 0.27% of patients,[12] while another systematic review reported clinically diagnosed opioid misuse or addiction in 3.3% of participants in studies that included patients with a history of substance misuse.[19] Current data show that the risk of opioid misuse is increased in patients with a history of substance misuse or mental disorders, males, younger patients, and those taking higher daily doses.[20 21] A more recent study in a non-selected population suggests that about 1 in 3 patients receiving long term opioid therapy for chronic pain met DSM criteria for addiction.[22] However, in a Norwegian cohort study of 245 000 opioid-naive patients starting treatment with weak opioids for non-malignant pain, the prevalence of persistent and of problematic opioid use was only 0.3% and 0.08% respectively[23]
- Sedation and cognitive impairment—Data are inconsistent but suggest this is minimal with stable long term doses. However, patients need to be cautioned about possible impairment when introducing or changing opioids or increasing doses[24]
- Despite a hypothesis that opioid use for non-cancer pain may be associated with an increased risk of type 2 diabetes, new data from 1.7 million opioid users in the UK found no such association.[25]

Check the box if the item applies. A score of 0-3 indicates low risk, a score of 4-7 indicates moderate risk, and a score of 8 or higher indicates high risk

ITEM	WOMEN	MEN
1. Family history of substance abuse:		
• alcohol	[ ] 1 point	[ ] 3 points
• illegal drugs	[ ] 2 points	[ ] 3 points
• prescription drugs	[ ] 4 points	[ ] 4 points
2. Personal history of substance abuse:		
• alcohol	[ ] 3 points	[ ] 3 points
• illegal drugs	[ ] 4 points	[ ] 4 points
• prescription drugs	[ ] 5 points	[ ] 5 points
3. Age between 16 and 45 years	[ ] 1 point	[ ] 1 point
4. History of preadolescent sexual abuse	[ ] 3 points	[ ] 0 points
5. Psychological disease:		
• attention deficit disorder, obsessive-compulsive disorder, bipolar disorder, or schizophrenia	[ ] 2 points	[ ] 2 points
• depression	[ ] 1 point	[ ] 1 point
TOTAL		

Opioid Risk Tool for clinical use to identify patients who may develop aberrant behaviours when prescribed opioids for chronic pain. Reproduced with permission of the authors[43]

What are the precautions?

Although there are generally no absolute contraindications to opioid use for managing chronic non-cancer pain, precautions are needed to minimise side effects and risks, such as those mentioned in the previous section, and in those with comorbidities. For example, prescribers should avoid or use only lower doses of morphine in patients with renal impairment.

Reduce risks of sedation and respiratory depression by avoiding or limiting use of other central nervous system depressants such as benzodiazepines, identifying patients with obstructive sleep apnoea,[26] and slowing up-titration of doses, especially with methadone because of its high inter-individual variability of half life and risk of accumulation.[27]

Other measures include adherence to treatment guidelines and pre-treatment assessment of risk of misuse and diversion for all patients (see next section). Identification of risk factors does not preclude opioid therapy, but requires additional safeguards for long term use, including participation in a prescription monitoring programme if available, possibly urine drug testing, opioid "contracts," and frequent review. Prescription of "abuse-deterrent formulations" is another useful precaution; such formulations rely on mechanical or pharmacological barriers to opioid extraction and subsequent parenteral use.[28]

The most common adverse effect of opioids in long term therapy is constipation, which is experienced by around 40% of patients taking opioids for chronic non-cancer pain.[29] Contrary to other adverse effects, tolerance to opioid induced constipation does not develop.

How do opioids compare with other drugs for chronic non-malignant pain?

Irrespective of the drug class used (opioids and non-opioid analgesics such as NSAIDs), randomised placebo controlled trials show that, although the drugs show statistically

Table 2 | Approximate equianalgesic oral and transdermal doses of opioids used for treatment of chronic pain*

Opioid	Equivalence to oral morphine 30 mg
Oral doses	
Dihydrocodeine	120 mg
Tramadol	150 mg
Tilidine	150 mg
Tapentadol	100 mg
Oxycodone	20 mg
Hydromorphone	4 mg
Buprenorphine	0.4 mg sublingual
Methadone, levomethadone	Wide variability, requires titration
Transdermal doses	
Buprenorphine	17.5 µg/hour
Fentanyl	12 µg/hour

The values given are usually mean values (also dependent on the commercial drug formulation) with considerable variability and are only a rough guide for careful individual titration.
*Modified from multiple sources, including *Goodman & Gilman´s The Pharmacological Basis of Therapeutics*, 12th ed (McGraw-Hill, 2011) and *Wall and Melzack's Textbook of Pain*, 5th ed (Elsevier, 2006).

Box 1 | Tips for patients

- Opioids are strong pain relieving drugs such as morphine, which can be prescribed as tablets, syrup, injections, or skin patches
- Some types of pain respond well to these drugs (such as cancer pain), but the drugs are not so effective in most chronic pain conditions, in particular with long term treatment
- Usually you need to take the drugs for a trial of about four weeks before your doctor will know if they are going to be helpful. The aim of this trial is to improve your level of functioning so that you can become more active at home, at work, and in your time off. If the trial shows that you cannot achieve these goals, then long term medication with opioids will not be useful to you and the treatment will need to be stopped
- It is important to remember that taking medicines to reduce your pain is only one part of managing your pain. Being involved in normal daily activities and participating in programmes that help improve your social, physical, or psychological functioning will be more important than if you just take a tablet; however, opioids may help you to achieve these goals
- You must keep your medicine where children and pets cannot reach it, preferably in a locked cupboard. Apart from your close family and your doctor(s), do not tell people you are taking these drugs. This is for your own protection against theft and robbery
- Medication that is lost, stolen, or misplaced cannot be replaced. No additional prescriptions can be given to "top you up" if you have used all of your painkillers before your next prescription is due

Box 2 | Opioid treatment agreement ("contract")

- Regular follow-up visits (initially frequent, then at least monthly)
- Prescriptions only from a single medical practitioner and one designated pharmacy
- Urine or serum drug screening when requested
- Explicit reasons for which opioid therapy may be discontinued—violation of a documented agreement, concomitant illicit drug use, repeated loss or theft of medication, unexplained escalation of dose or request for opioids from other sources

significant pain reduction, the clinical effect is often only minor to moderate.[30 31] Direct comparisons between non-opioids and opioids are rare and contradictory: a randomised controlled trial in patients with osteoarthritis showed controlled release tramadol to be as effective and as well tolerated as sustained release diclofenac,[32] whereas two other randomised controlled studies showed celecoxib to be more effective than tramadol with fewer adverse events in patients with chronic low back pain.[33] In both studies, the duration of treatment was only six weeks. Obviously, more head-to-head trials are needed with other opioids and for conditions other than beyond osteoarthritis and low back pain. As the effects of all analgesics are only moderate, selection of the most suitable analgesic should be tailored to each patient's risk factors. For instance, patients at high risk of complications from NSAIDs (for example, those with a history of gastrointestinal ulcers, with renal insufficiency, or using warfarin) may be treated with an opioid, while patients at risk of complications with opioids (such as elderly frail patients prone to falls) may be better treated with NSAIDs.

How cost effective is the use of opioids for treating chronic pain of non-malignant origin?

Although a couple of cost effectiveness analyses, usually performed or sponsored by the pharmaceutical industry, show cost reduction from the payer's perspective,[34] the overall pharmacoeconomic evaluation is negative: use of opioids in chronic pain increases the overall costs of healthcare due to increased disability, cost of medical consults and drug supplies, and work absences, and reduced social functioning.[35-37] Also there are the societal costs of prescription opioid misuse, estimated to exceed $56bn in the US in 2007.[38]

How are opioids taken and monitored for treating chronic pain of non-malignant origin?

The following approach to prescribing opioids is recommended, based on a compilation of multiple guidelines[12 24 39-42] and the authors' opinion and experience.

Before considering opioids

- Make all reasonable attempts to achieve a psychological assessment and a physical diagnosis of the cause of pain
- Ideally patients should have multidisciplinary and multimodal pain management
- Carefully document the patient's severity of pain and impairment of function, psychiatric status, history of substance and alcohol use, and addiction risk (for example, with the Opioid Risk Tool (see fig)[43])
- Discuss the risks and benefits of long term opioid therapy with the patient. Agree on treatment goals with an emphasis on improvement of the patient's quality of life and function—that is, pain reduction as well as dimensions such as sleep, mood, work, social and recreational activities
- Taper off and stop benzodiazepines before starting opioid treatment if possible.

Initiating opioid therapy

- Advise patients that treatment will start with a trial period of about four weeks. Agree on realistic and achievable treatment goals, including pain reduction and improvement in quality of life and function (such as sleep, mood, work, and social and recreational activities). Deciding not to proceed with treatment is also a valid outcome for such a trial
- Obtain informed consent, including the risk of drug dependence, opioid induced hyperalgesia, and tolerance. Caution the patient that the use of other central nervous system depressants, alcohol, or illegal drugs with opioids can cause serious side effects, including overdose and death. Inform patients and caregivers that withdrawal symptoms can occur if an opioid is stopped suddenly and how to handle missed doses. Counsel patients about safe use and storage (see box 1). Discuss potential limitations with regard to opioid supply while travelling, in particular

with regard to international travel in countries with restrictions on availability and importation of opioids
- Use of an opioid treatment agreement ("contract") outlining the rights and responsibilities of the doctor and the patient may be helpful (see box 2)
- Co-prescribe laxatives. The role of a combination of prolonged release oxycodone and naloxone in the prevention and management of opioid induced constipation is still a matter of debate, but this approach can decrease the need for laxatives and additional medications, particularly in vulnerable groups such as older people or those with advanced cancer[44]
- Titration of appropriate doses of long acting opioids should be accompanied by regular review of the treatment goals. Most guidelines agree on maximum doses in the range of 100 mg of morphine equivalent, at which titration should be stopped or requires intense assessment and monitoring. During titration, advise patients to avoid driving and using heavy machinery until sedation and impaired cognition or psychomotor abilities are excluded
- Rotation to another opioid (see table 2 for equianalgesic doses of opioids) might be indicated in cases of unacceptable side effects or insufficient effectiveness (for example, because of rapid development of tolerance).

Monitoring

- Ensure that patients adhere to your treatment plan
- Regularly evaluate the "four As"—analgesia, activities of daily living, adverse events, and aberrant drug taking behaviour
- Ensure compliance with opioid "contract," including single prescriber, designated pharmacy, and no unauthorised increase of dose (reconcile medication against prescriptions)
- Re-evaluate patients' underlying medical condition if symptoms change over time.

Ceasing opioid therapy

- Long term opioid therapy should not be seen as a lifelong therapy; to exit an opioid therapy is often more appropriate than maintaining the loop forever
- Cease opioid therapy if treatment goals are not achieved or if aberrant drug taking behaviour is identified
- Discontinue opioids by tapering the dose over an extended period to avoid withdrawal symptoms. If withdrawal symptoms such as restlessness, diarrhoea, and irritability do occur, reduce speed of tapering or support patient by use of clonidine[45]
- Aberrant drug taking behaviour (in particular, drug supply from multiple sources, use of parenteral routes, diversion, repeated requests for replacement of lost or stolen medication) should lead to referral to a drug misuse service.

Case outcome

In the case described above, the doctor should advise the patient that opioids are not likely to be helpful in his case. The doctor should discuss a multidisciplinary and multimodal approach with emphasis on physiotherapy/paced physical activation and possibly cognitive behavioural therapy. This will be more likely to restore function than simple prescribing of opioids, but it may require referral to an appropriate pain service.

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References are in the version on bmj.com.

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ANSWERS TO ENDGAMES, p 42

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CASE REPORT

Metabolic alkalosis in a patient with dyspnoea

1 This patient has post-hypercapnic metabolic alkalosis, which occurs when the carbon dioxide level in the blood drops rapidly owing to an increased respiratory rate in a patient with compensated chronic retention of carbon dioxide. In this case, hyperventilation was caused by a combination of anxiety, relative hypoxia, and concomitant pneumonia.
2 Furosemide.
3 No.

STATISTICAL QUESTION

What is per protocol analysis?

Answer *d* would result in a trial participant being included in the per protocol analysis, whereas *a*, *b*, *c*, and *e* would not.

PICTURE QUIZ

Forearm injury in a 5 year old boy

1 The radiographs show a minimally displaced proximal third ulna diaphyseal fracture and a radial head dislocation. The eponymous term for this injury is a Monteggia fracture of the forearm.
2 A line drawn along the long axis of the radius should bisect the capitellum on any view.
3 Ensure the injury is isolated, closed, and neurovascularly intact.
4 The patient should be managed in the emergency department and invariably will be admitted for surgical stabilisation.