PAIN MANAGEMENT: PART 2

The second of a three-part feature comprising expert answers to readers' questions on managing pain in primary care

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Q. What are the dangers of long-term tramadol?

A Tramadol is an opioid, hence all the usual risks of long-term opioids apply, including constipation, nausea, dependence, intolerance and endocrine/immune suppression. Like all opioids, they may distort the sleep/wake cycle, causing patients to request "sleeping tablets". One in 10 people who take tramadol complain of nausea or feeling dizzy. One in 100 people report constipation, dry mouth, headaches, sleepiness, sweating, tiredness and vomiting. In addition, the noradrenergic effects may cause hallucinations/confusion, especially in the elderly.

There are two main dangers with tramadol. Patients who take a few extra to cover an escalation in pain may find they fit due to an accumulation of a pro-epileptogenic metabolite at doses above 400mg/day. It should also be avoided in patients with history of attempted suicide, as recommended by the Advisory Council on the Misuse of Drugs (ACMD), based on concerns about the misuse of tramadol and an increase in the number of deaths involving the drug, which increased from 83 in 2008 to 154 in 2011.

Unfortunately, tramadol also shows marked and significant interactions, particularly with antidepressants, adding complexity to the management of chronic pain patients.

It may be worth considering the opioid analgesic meptazinol as an alternative. This is a partial u-opioid receptor agonist. Its mixed agonist/antagonist activity affords it a lower risk of dependence and abuse compared with morphine. It also has a shorter onset and duration of action. Meptazinol seems to play a useful role in providing relief where something stronger than codeine is indicated, but where one would want to avoid tramadol or stronger opioids such as morphine, as in the elderly patients for instance. In practice it does not seem to be associated with dose escalation problems. Don't expect too much research on this very useful drug, however, as it is off patent.

Q. What is the latest evidence on NSAIDS and cardiac risk

A A study by the Coxib and traditional NSAID Trialists' (CNT) collaboration published last year (*Lancet* 2013; 382: 769–79) highlighted the risk of major vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death), major coronary events (non-fatal myocardial infarction or coronary death) and gastrointestinal complications associated with NSAIDS.

Major vascular events were increased by about a third by a coxib or diclofenac – chiefly due to an increase in major coronary events. Ibuprofen also significantly increased major coronary events, but not major vascular events. Compared with placebo, of 1000 patients allocated to a coxib or diclofenac for a year, three more had major vascular events, one of which was fatal.

Naproxen did not significantly increase major vascular events. Vascular death was increased significantly by coxibs and diclofenac, but not significantly by ibuprofen or naproxen. The proportional effects on major vascular events were independent of baseline characteristics, including vascular risk. Heart failure risk was roughly doubled by all NSAIDs.

All NSAID regimens increased upper gastrointestinal complications.

The take home messages are:

- **Nonselective NSAIDs:** With exception of naproxen, these agents increase the risk of having a myocardial infarction. This is especially seen with high dose of ibuprofen and diclofenac.
- **Selective NSAIDs:** There is no significant increase in risk of myocardial infarction or stroke with celecoxib, but there are no long term studies.
- **Partially selective NSAIDs,** eg meloxicam: not certain

Q. What drugs are most effective for neuropathic pain?

A Treatment of neuropathic pain and its cause should begin early. The medications shown to have the best efficacy in the management of neuropathic pain include tricyclic antidepressants (TCAs), e.g. amitriptyline, gabapentinoids (such as gabapentin and pregablin) and serotonin-noradrenaline reuptake inhibitors (SNRIs), such as duloxetine. Benefit from TCAs is independent of their antidepressant effects.

Neuropathic pain can be very difficult to control. One should always do a careful, slow titration of any first line agent, but be aware that it is impossible to predict who will respond to which drug. Efficacy will vary from individual to individual, even when the diagnosis appears to be the same. All of the anticonvulsant drugs used for neuropathic pain have slightly different mechanisms of action, so some patients will do better with a TCA, some with a gabapentinoid and few with a sodium channel blocker such as mexileitine or lamotrigine.

Although amitriptyline is the easier drug to use (once-daily dosing at night, handy sedative effect), patients may complain of feeling sleepy and sedated. Changing the timing of doses to 12 hours before waking can be helpful. If the patient fails to get the desired effect at doses up to 50mg, there's little likelihood of 75mg being better. It makes sense to reduce the dose of the tricyclic back to 25mg and add in a gabapentinoid slowly. Patients may need at least 6-8 weeks on a stable dose before they really see a benefit, so counselling is essential. Again, if a combination isn't helping, or isn't tolerated, don't wait – refer the patient to a pain clinic.

TCAs can be problematic in depressed patients because of the harmful effect in overdose, and the presence of unwanted side-effects at the higher doses required for antidepressant as compared to neuropathic action. The use of the SNRI antidepressants duloxetine and venlafaxine is often preferable when a combination of antineuropathic and antidepressant effects is required. These drugs that are safer in overdose and often relatively better tolerated than the TCAs. Topical treatments, like lidocaine plasters or capsaicin may be useful for those with very localised pain, or in whom side effects are a problem.

It is very common to treat patients with neuropathic pain with more than one anti-neuropathic medication. This is because several classes of drug work on different postulated mechanisms, and it is often difficult to achieve adequate pain relief with single drug. There is in fact level 1 evidence that mixing a TCA with a gabpentinoid is likely to provide useful additional effects over single drug administration. This approach has official backing in the latest Scottish guidance from SIGN (http://www.sign.ac.uk/pdf/SIGN136.pdf)

Numbers needed to treat (NNTs) for neuropathic pain treatments are shown in Figure 1.

FIG 1. NNT OF MEDICATIONS USED FOR NEUROPATHIC PAIN

Drug	NNT	Titration	Notes	Side Effects
TCA	2.5-3	2-15 wks	Antidepressant, cheap	Anticholinergic
Duloxetine	4-5	None	Anxiolytic, antidepressant	Few
Venlafaxine	4-5	3-5 wks	Antidepressant	Few
Gabapentin	3.5-4.5	1.5-6 mo	Min. drug interactions	Dizzy/sleepy
Pregabalin	3.5-4.5	1-2 wks	Min. drug interactions	Dizzy/sleepy
Methadone	?	Variable	Opioid, cheap	Opioid, drug interactions
Ketamine	?	1-4 wks	Opioid sparing	Hallucinations
Tramadol	3.8	4-8 wks	For Diabetes, PHN	Anticholinergic
Carbamezapine	1.7	1-4 wks	For Trigeminal neuralgia	Drug interactions
Lidocaine/Mexilitine	4	None	IV trial then po	Cardiac, neurologic
Capsaicin	?	none/days	Topical	Burning, redness
Cannabinoids	?	none/days	For MS, allodynia	GI, drowsiness
Clonidine	?	none/days	Effective IT, topical	Hypotension

Q. For patients who require trial of strong opioids for non-cancer pain, is there any we should use first line?

A The long-term risks of strong opioids are being increasingly recognised, both in primary and secondary care settings. Use of strong opioid in non-cancer pain is now no longer generally recommended in primary care settings due to increasing evidence of high NNTs (see Table 1), poor QoL outcomes (see box below), diversion and increased mortality above about 100mg- 120mg of morphine. Following concerns about long-term opioid therapy, it is being increasingly recommended that opioids are used mainly as rescue medications for breakthrough for all types of pain not controlled with other pain killers. For example in the new NICE guidelines for neuropathic pain, tramadol is only recommended for breakthrough neuropathic pain rather than maintenance therapy

LONG TERM RISKS OF OPIOID THERAPY (FRYNHAGEN ET AL 2013)

- About a 3-fold increase in falls leading to fractures
- Respiratory depression
- Deaths—Increasing use of opioids for chronic non-cancer – pain is paralleled by rapidly rising numbers of deaths related to prescription opioids
- Negative endocrine effects, mainly via the – hypothalamic-pituitary-adrenal axis, leading to opioid – induced androgendeficiency
- Opioid induced hyperalgesia
- Potential for abuse and opioid addiction—figure range from 3–33%
- Sedation and cognitive impairment especially with dose changes

Starting patients on long-term opioids may have significant implications in terms of their effect on the patient's immune system and endocrine hormones. The British Pain Society has issued guidelines for opioid prescribing and hormone testing for patients on long-term opioids. There is an increasing trend to gain formal consent from patients after discussing the risks and benefits of using long-term opioids.

The risk of opioid diversion should be assessed in each patient, for example looking for past history of addictive problems, inappropriate dose escalation and drug-seeking behavior, particularly from multiple providers.

In summary, there is no one drug that can be recommended and treatment should be individualized to each patient, though buprenorphine is generally not associated with the problems associated with most other opioids.

TABLE 1. RESULTS OF A 2009 COCHRANE REVIEW OF 10 CONTROLLED TRIALS COMPARING OPIOID WITH PLACEBO OR NO TREATMENT FOR CHRONIC NON-CANCER PAIN IN 2268 PARTICIPANTS

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).

NEXT ISSUE

Answers to more of your questions on pain management

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