Prescribing tramadol appropriately

KEY MESSAGES:

- Tramadol is an atypical opioid, used for moderate pain when paracetamol and/or a NSAID is not adequate; alternative options are codeine or dihydrocodeine
- Tramadol is associated with less risk of respiratory depression and constipation than codeine and dihydrocodeine, but has an increased risk of serotonin toxicity
- There is relatively weak evidence supporting the use of tramadol for patients with neuropathic pain

Tramadol is an atypical analgesic

Tramadol is a synthetic, atypical, centrally-acting analgesic that binds to the μ-opioid receptors and also inhibits the reuptake of serotonin and noradrenaline, resulting in both opioid and antidepressant-like effects.[1] Tramadol is considered a "weak opioid" and is a prescribing option at Step two of the analgesic ladder, alongside codeine and dihydrocodeine (see: "The principles of managing acute pain in primary care").

There are no robust studies suggesting that tramadol provides either more or less analgesia than codeine or dihydrocodeine. Like codeine and dihydrocodeine, tramadol is metabolised by CYP2D6, which produces a metabolite that has substantially greater affinity for the μ-opioid receptor than its parent drug.[2] Eight to 10% of people of European descent are poor CYP2D6 metabolisers and 3 to 5% are ultra-rapid metabolisers;[2] there is no published data for Māori or Pacific peoples. People who are poor CYP2D6 metabolisers are likely to experience reduced analgesia with tramadol (and codeine) and ultra-rapid metabolisers may be more sensitive to adverse effects.[2]

Tramadol is associated with both opioid and antidepressant-like adverse effects

Tramadol is associated with adverse effects seen in both opioid and antidepressant classes of medicine (Table 1).[3] Tramadol has less risk of respiratory depression and constipation than codeine and dihydrocodeine because it is only a partial μ-opioid receptor agonist.[2] However, nausea, vomiting and dizziness can be expected in at least 10% of patients taking tramadol.[4]

There is an increased risk of serotonin toxicity with the use of tramadol and it is contraindicated in patients with uncontrolled epilepsy or those who have taken a monoamine oxidase inhibitor in the last 14 days.[5] Caution is advised when considering tramadol in combination with other serotonergic medicines, and if the combination is prescribed, patients should be advised to cease treatment if they develop symptoms of serotonin syndrome, e.g. neuromuscular or autonomic effects or changes in mental state.[5]

Tramadol should also be used cautiously in patients with impaired respiratory function, e.g. asthma, chronic obstructive pulmonary disease and sleep apnoea, and in patients with hypotension, shock, impaired consciousness or obstructive bowel disorders.[5] If tramadol is prescribed to a patient taking warfarin, close monitoring of INR levels is recommended due to an increased risk of bleeding, particularly during the first week of treatment.[6]

Tramadol is contraindicated in children aged under two years due to the limited amount of safety and efficacy data.[7] Liquid tramadol is sometimes given to children in a secondary care setting for post-operative pain; care is required to avoid over-dose as two strengths are available, i.e. 10 mg/mL and 100 mg/mL, however, these formulations are not subsidised for use in the community.[7]

Prescribing tramadol to minimise adverse effects

The usual dose of tramadol is 50–100 mg per dose, with a maximum daily dose of 400 mg, and at least four hours between doses.[5] Older patients are most at risk of developing tramadol-related adverse effects, in which case the maximum daily dose should be reduced to 300 mg.[5] In patients with hepatic or renal dysfunction, who may have reduced elimination of tramadol, a low starting dose of modified-release tramadol, e.g. 50 mg, with titration to effect and 12-hour dosing is appropriate;[3,4] controlled-release tramadol should be avoided in these patients.[5] Tramadol should be avoided in patients with severe renal dysfunction, i.e. a creatinine clearance < 10 mL/minute.[5]

If patients experience nausea with the use of tramadol, consider lowering the dose and concurrently using paracetamol (see below) or switch the patient to codeine, dihydrocodeine or a NSAID. Modified-release tramadol may be associated with fewer adverse effects in some patients.[3]

Use paracetamol concurrently

The concurrent use of paracetamol with tramadol or codeine is more effective than tramadol or codeine alone.[2] Co-prescribing of paracetamol is an effective and widely used strategy for reducing tramadol and codeine use thereby improving patient safety and providing pain relief as these Step 2 analgesics are withdrawn.

When is tramadol preferred over codeine or dihydrocodeine?

Tramadol is associated with a decreased risk of respiratory depression and is therefore often preferred over codeine or dihydrocodeine in patients who are at increased risk of breathing difficulties, e.g. for musculoskeletal pain in a person with chronic obstructive pulmonary disease (COPD).[2] Tramadol

Table 1: The most common and most serious adverse effects associated with tramadol use[1]

Common adverse effects*	Serious adverse effects†
■ Nausea and vomiting	■ Serotonin syndrome
■ Dizziness	■ Seizures
■ Constipation	■ Respiratory depression
■ Autonomic effects, e.g. dry mouth, perspiration	■ Increased intracranial pressure
■ Headache	■ Anaphylactoid reactions
■ Sedation	
■ Fatigue	

* Adverse effects occurring in at least 1 in 100 patients

† Adverse effects with an approximate prevalence of 1 in 10,000 patients

may also be preferred over codeine or dihydrocodeine in patients with a history of constipation or in those taking anticholinergic medicines.

There is weak evidence that tramadol is effective in patients with neuropathic pain

Tramadol is sometimes prescribed as a second-line medicine to patients with neuropathic pain,[8] although the evidence supporting this practice is weak.[9] It is recommended to use a validated tool, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), to diagnose or exclude neuropathic pain. If neuropathic pain is present, the first-line pharmacological options would be a tricyclic antidepressant, gabapentin* or carbamazepine, which may be used in combination with an analgesic for nociceptive pain. In this scenario, it may be reasonable to select tramadol, in preference to codeine or dihydrocodine, if a Step 2 analgesic is required.

Further information on neuropathic pain, including a downloadable LANSS questionnaire, is available from: "Managing patients with neuropathic pain" **https://bpac.org.nz/BPJ/2016/May/pain.aspx**

Stopping tramadol

As with any opioid, tramadol should be used for the shortest possible time, at the lowest effective dose, with a plan in place to reduce and withdraw treatment. Tramadol may have less potential for misuse and dependency than other opioids as it is an atypical analgesic, however, the same prescribing cautions should be applied to tramadol as to other opioids to minimise the risk of inappropriate use.[1, 10]

Patients who have been taking an opioid for a short period of time for acute pain, e.g. one to two weeks, can usually stop it abruptly without the need for tapering the dose. However, a slower withdrawal may be considered for patients who have been taking frequent, higher doses.[11] There is no specific guidance for a structured tapering regimen for short-term use of tramadol, but a pragmatic approach would be to reduce the dose by 25–50% each day. Ensure that when tramadol is withdrawn (either abruptly or tapered), analgesic cover is provided by concurrent use of paracetamol or a NSAID, until the pain is manageable without pharmacological treatment.

References

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* From 1 May, 2018, pregabalin will become fully subsidised, making it an additional option for treating neuropathic pain. Prescribing restrictions will also be removed from gabapentin; bpac^{nz} will be publishing an article on these changes.

This article is available online at:
www.bpac.org.nz/2018/tramadol.aspx