

## TRAMADOL - SAFE PRESCRIBING - CONSIDER THE RISKS

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- ▶ UNDERSTAND THAT TRAMADOL CAN CAUSE SEIZURES
- ▶ BE AWARE OF THE RISKS OF SEROTONIN SYNDROME
- ▶ TAKE SPECIAL CARE WITH OLDER ADULTS
- ▶ DISCUSS POTENTIAL ADVERSE EVENTS BEFORE PRESCRIBING
- ▶ REMEMBER TRAMADOL IN AN OPIOID; IT HAS BEEN ASSOCIATED WITH DEPENDANCE AND WITHDRAWAL
- ▶ TAKE SPECIAL CARE WITH CHILDREN

Tramadol is indicated for the relief of moderate-to-severe pain.<sup>1,2</sup> It is a centrally-acting synthetic analgesic with opioid-like effects and serotonin and noradrenaline reuptake-inhibitor properties.<sup>3</sup> The combined effect of opioid and antidepressant-like properties can lead to adverse effects observed with both types of agents.

Tramadol is usually considered if other 'Step 2' (WHO pain ladder category) analgesics such as codeine are not tolerated or contraindicated.<sup>3,4</sup> The same caution is required when prescribing tramadol as with opioid analgesics.

Although tramadol is associated with fewer of the typical opioid adverse effects (eg respiratory depression, constipation and addiction potential), other effects such as nausea, vomiting and dizziness are common, and can be problematic.<sup>3,5,6</sup> Some patients find that they experience fewer side effects with the slow-release tramadol preparations.<sup>3</sup>

### UNDERSTAND THAT TRAMADOL CAN CAUSE SEIZURES

The activity of tramadol on serotonin and noradrenaline transmission is associated with lowering of the seizure threshold.<sup>2</sup> The risk of seizures increases further with:

- concurrent treatment with other medicines that lower the seizure threshold, eg some antidepressants and antipsychotics
- a history of seizures - tramadol is contraindicated in patients with uncontrolled epilepsy<sup>2</sup>
- doses over 400 mg per day<sup>1</sup>

A quarter of adverse drug reaction reports pertaining to tramadol involve convulsions.<sup>7</sup>

### BE AWARE OF THE RISKS OF SEROTONIN SYNDROME

As with other serotonergic medicines, tramadol is associated with serotonin syndrome. Symptoms can include hyperthermia, agitation, slow continuous horizontal eye movements (referred to as ocular clonus), dilated pupils, tremor, akathisia, deep tendon hyperreflexia and inducible or spontaneous muscle clonus.<sup>8</sup>

There is an increased risk of serotonin syndrome when higher doses of tramadol are used or when tramadol is combined with other serotonin-enhancing medicines. These medicines include:

- antidepressants such as the selective serotonin reuptake -inhibitors (SSRIs) eg paroxetine, citalopram and fluoxetine, concomitant treatment should be undertaken with caution
- tricyclic antidepressants (TCAs) eg amitriptyline, nortriptyline, concomitant treatment should be undertaken with caution
- MAOI-type antidepressants eg moclobemide, phenelzine

Other medicines that have been associated with serotonin syndrome include pethidine, lithium, St John's Wort, levodopa, and illicit drugs such as cocaine and methamphetamine.

Encourage patients to report any symptoms of serotonin syndrome. If it is suspected, withdrawal of serotonergic medicines usually brings about rapid improvement.<sup>1</sup> In most cases, serotonin syndrome presents within 24 hours of a change to, or initiation of, a serotonergic medicine.<sup>8</sup>

**Note:** Some patients with pain syndromes have co-morbid depression and require analgesics and antidepressants.

## TRAMADOL

Prescribers should bear in mind the potential risks of serotonin syndrome and seizures when making a clinical decision to use tramadol. If tramadol is clinically indicated for these patients, regularly ask about symptoms of serotonin syndrome, and ensure the dose of tramadol is within current recommendations.<sup>9</sup>

### TAKE SPECIAL CARE WITH OLDER ADULTS

Most of the spontaneous reports of adverse reactions pertaining to tramadol, involve patients over 80 years of age.<sup>7</sup> It is recommended that lower doses are prescribed to patients over 75 years, with the maximum daily dose no greater than 300 mg.<sup>1,3</sup> This is due to elevated serum concentrations of tramadol and delayed elimination in older adults.<sup>1</sup>

Patients with renal or hepatic insufficiency may have delayed elimination of tramadol, for these patients, consider increasing the dosing interval. Titrate the dose to effect, start low (50 mg) and go slow; 12 hourly dosing may be sufficient. Tramadol is not recommended for patients with severe renal (CrCl < 10 mL/min)<sup>9</sup> or hepatic impairment.<sup>1</sup>

### TAKE SPECIAL CARE WITH CHILDREN

Tramadol is contraindicated in children less than two years of age due to the limited data on efficacy and safety in this patient group.<sup>10</sup> In April 2017, the FDA issued a warning that recommends against use of tramadol in breastfeeding women because of possible harm to infants. For teens aged 12 to 18 years there is a warning against using tramadol if there is a history of obesity, obstructive sleep apnoea, or severe lung disease. In particular tramadol should not be given to children or adolescents as a pain medication after surgery to remove the tonsils or adenoids.<sup>10,11,12</sup>

**Australia and America do not recommend using tramadol in children under the age of 12 and 17, respectively. This was considered by MARC who considered there is a role for tramadol use in children.**<sup>12</sup>

### DISCUSS POTENTIAL ADVERSE EVENTS BEFORE PRESCRIBING

Most prescribers will be familiar with patients who feel strange and don't function well with tramadol. This could be due to a genetic predisposition.<sup>13</sup>

The most common adverse effects of tramadol are dizziness, nausea, vomiting, constipation, increased sweating and fatigue.<sup>1</sup> Tramadol has been associated with elevated liver enzymes and rash. There have been reports of mood alterations including mania and auditory hallucinations<sup>14,15</sup> and delirium in some patients.

Due to the sedative effects of tramadol, patients should

avoid driving or operating dangerous machinery if they are affected.<sup>1</sup> For patient information, there is a SafeRx® patient guide available on [www.saferx.co.nz](http://www.saferx.co.nz).

Tramadol should be administered cautiously in patients at risk of respiratory depression. Profound sedation, respiratory depression, coma, and death may result from the concomitant use of tramadol with benzodiazepines or other CNS depressants (eg non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids and alcohol).<sup>1</sup>

The safety of tramadol has not been established in pregnancy, or during labour. Tramadol is not recommended during breastfeeding.<sup>1,11,16</sup>

Some patients who have been previously stable on warfarin experience an increase in INR when tramadol is added. Patients who are taking warfarin should avoid tramadol where possible; if tramadol is unavoidable, monitor the INR closely when tramadol is added or discontinued.<sup>1,17</sup>

### TRAMADOL IS AN OPIOID; IT HAS BEEN ASSOCIATED WITH DEPENDENCE AND WITHDRAWAL

There is an increased risk of fatal overdose when tramadol is taken with other central nervous system depressants such as alcohol and benzodiazepines. Tramadol is contraindicated in patients who are acutely intoxicated with alcohol, hypnotics, analgesics, opioids or psychotropic drugs.<sup>1,2</sup> The Federal Drug Administration (FDA) in the United States have advised prescribers to avoid tramadol if patients are suicidal or addiction-prone.<sup>18</sup>

The opioid component of tramadol could make some patients develop tolerance; sudden withdrawal may lead to side effects which include agitation, anxiety, insomnia, tremor, pyrexia and chills.<sup>1</sup>

**Note:** There are no clinical studies investigating efficacy and safety of chronic tramadol use beyond 6 months.<sup>1</sup>

Which preparation?

Preparation	Doses available	Recommended dose
Immediate release	50mg capsules	Up to every 4-6 h as required Max 400mg in 24 h
	Oral liquid 100mg/mL*	
Slow release	50mg*, 100mg, 150mg, 200mg, 300mg* SR tablets	Every 12 h

\*Not funded in the community

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## TRAMADOL

Tramadol immediate release capsules may be used alone, or for breakthrough pain relief with tramadol SR tablets.

### For moderate pain:

Tramadol 50-100mg capsules twice to three times daily

OR Tramadol SR tablets 100mg twice daily

### For more severe pain:

Tramadol 100 mg capsules every 4-6 hours to a maximum of 400 mg in 24 hours

OR Tramadol SR 200mg tablets twice daily

Sometimes a maximum daily dose of 600mg is used in secondary care; this dose should not be continued on discharge.

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