

TRAMADOL - SAFE PRESCRIBING - CONSIDER THE RISKS!

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- ▶ CAN CAUSE SEIZURES – FATALITIES HAVE BEEN REPORTED
- ▶ RISK OF SEROTONIN SYNDROME IN COMBINATION WITH OTHER MEDICINES
- ▶ COMBINATION WITH WARFARIN CAN INCREASE INR
- ▶ MILD OPIATE – HAS BEEN ASSOCIATED WITH DEPENDENCE/WITHDRAWAL SYNDROMES AND RESPIRATORY DEPRESSION
- ▶ ADVERSE EVENTS COMMON – OFTEN PSYCHIATRIC

Tramadol is a synthetic opiate analgesic with serotonin and noradrenaline reuptake inhibitor properties which enhance the analgesic effect via pain transmission in the spinal cord. The combined effect of opiate and antidepressant-like properties leads to the adverse effects that are observed with both types of agents.

The same caution is required when prescribing tramadol as with any other opiate analgesic.

Tramadol features significantly in adverse drug reaction reporting compared to its usage, which is restricted currently by its lack of funding on the PHARMAC schedule. There are more reactions reported by tramadol than with any other opiate except morphine, and more psychiatric and neurological reports than any other opiate.

Tramadol's activity on serotonin and noradrenaline transmission is associated with lowering of the seizure threshold and increasing the risk of serotonin syndrome. These adverse events are observed with high doses/ overdose, as well as at normal doses when it is combined with antidepressants and other serotonin enhancing agents.

RISK OF SEIZURES

There have been many case reports of seizures in New Zealand with tramadol¹. In a report of 12 cases of seizures associated with tramadol, risk factors included concurrent treatment with other medicines that lower the seizure threshold, e.g. antidepressants and antipsychotics. **Seizure activity is increased at doses of 400mg or more per day.** There have been reports of fatalities secondary to seizure activity.

SEROTONIN SYNDROME – IMPORTANT INTERACTIONS

Tramadol has been associated with serotonin syndrome when used with other agents that also act on serotonergic pathways. Symptoms can include: agitation, ataxia, increased sweating, diarrhoea, fever, hyperreflexia, myoclonus, or shivering. Agents that have been associated with this reaction include: antidepressants such as the selective serotonin reuptake inhibitors (e.g. paroxetine, citalopram and fluoxetine), tricyclic antidepressants (e.g. amitriptyline), MAOI-type antidepressants and venlafaxine. There have also been reports with carbamazepine and the newer antipsychotic agents such as olanzapine^{2,3}. Patients with pain syndromes often have co-morbid depression - because this population is often treated with antidepressants, caution is required when prescribing.

Other agents that have been reported to be associated with serotonin syndrome include: St John's Wort, medicines for Parkinson's disease (amantadine, bromocriptine, cabergoline, levodopa, pergolide and selegiline), illicit drugs (e.g. cocaine, methamphetamine, LSD), anti-migraine agents (e.g. sumatriptan) and other medicines including: pethidine, lithium carbonate, bupropion and sibutramine.

WARFARIN

Other interactions associated with tramadol include an increased INR for some patients stabilised on warfarin. This interaction appears to be associated with patients that have defective cytochrome P450 2D6 metabolism⁴.

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TRAMADOL

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OPIATE EFFECTS

The most common adverse effects associated with tramadol relate to its opiate actions. These are primarily: dizziness, nausea and somnolence⁵. More serious opiate-related adverse events include: respiratory depression, dependence and withdrawal symptoms; some patients have developed physical dependence^{6,7}.

Tramadol and its metabolites are cleared via renal excretion. There have been case reports of respiratory depression in patients with impaired renal function. Tramadol appears to have a lower abuse potential when compared to other opiates, but **there have been reports of abuse and intoxication**⁶. Like other CNS agents, the risk of fatal overdose is increased if tramadol is ingested with other CNS depressants such as alcohol and benzodiazepines⁸.

ADVERSE EVENTS COMMON – OFTEN PSYCHIATRIC

Most prescribers will be familiar with patients who feel strange and don't function well on tramadol; significant confusion and depersonalisation have been frequently reported⁸. Elevated liver enzymes and rashes may also occur, with a spectrum of other side effects affecting many organ systems. There have been rare reports of mood alterations including mania and auditory hallucinations^{9,10}. Like all opiate agents, tramadol can induce delirium in susceptible patients⁸.

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