DrugWatch Information Sheet

Tramadol

UK & IRELAND DrugWatch

Version: 1.0.1
Original version: 10/12/2017
Revision date: 04/02/2018

Drug overview: Tramadol is a centrally acting analgesic structurally related to codeine. It has multiple actions: after entering the body it breaks down (metabolises) mainly into O-desmethyltramadol which acts on opioid receptors and also affects levels of serotonin and noradrenaline. It is approximately as potent as codeine and used to treat both acute and chronic pain.[1]

Chemical name: Tramadol hydrochloride, (±)-*cis*-(2-dimethylaminomethy)-1-(3-methoxyphenyl)-cyclohexanol.

Drug class: Tramadol is an atypical synthetic opioid analgesic.

Street/brand names: Tramadol, trams, trammers, trammies or brand names such as Zydol.

Background: Tramadol was first synthesised in 1962 by Grünenthal GmbH in Germany.[2]

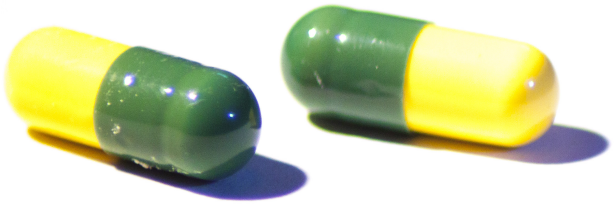

Fig. 1: 50mg Tramadol capsule

Routes of administration: Tramadol is marketed as the hydrochloride salt and is available as tablets, capsules, sub-lingual drops, sustained-release formulations for oral use, intranasal and rectal (suppository) formulations and solution for intramuscular, intravenous and subcutaneous injection.[3,4]

Legal status: Tramadol was controlled under the Misuse of Drugs Act 1971 as a Class C Drug in June 2014.

Onset, duration and half-life: Tramadol is rapidly and almost completely (>90%) absorbed after oral, rectal and intramuscular administration.[1,3] Its analgesic effect takes place about one hour after oral administration and peaks after two to three hours, lasting for about six hours.[4] Peak plasma concentrations after oral, rectal and intramuscular administration are reached in 1-2 hours, 3 hours and 45 minutes respectively.

Sustained-release formulations release over 12 hours, reaching peak concentration after 4.9 hours. Tramadol and its metabolites are mainly excreted in urine (90%) and faeces (10%): about 30% of an oral dose is excreted unchanged in the urine, and about 60% in the form of metabolites (mainly O-desmethyltramadol).

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The mean elimination half-life of tramadol is about 6 hours regardless of route of administration, and about 8 hours for O-desmethyltramadol.[1,3] Half-lives may be prolonged in people with decreased liver or kidney function: in patients with severe liver cirrhosis the elimination half-life was extended to a mean of about 13 hours, while extreme values reached up to 22 hours.[5]

Dosage and route of administration: The recommended daily dose is in the range of 100-400mg and the stated maximum dose should not exceed 400mg per day.[3] A search of online user reports found that oral administration is the most favoured by users. Users report that intravenous or nasal use of tramadol does not result in any 'rush' or increased opioid effects[6,7,8] and that nasal use can result in significant nasal 'drip' without any additional effects. Online users debate the comparative potency of rectal versus oral administration.[9]

Fig. 2 Tramadol packaging

Effects:

Physical [1,3,5]	Psychological [10,11,12]
Pain relief, CNS depression, dizziness, nausea, drowsiness, vomiting, itching, increased sweating, dry mouth, dependency, pupil constriction (at higher doses) or dilation. In larger doses: tachycardia (rapid heart rate), agitation, seizures, flushing, serotonin syndrome*, cardiovascular collapse, coma, respiratory depression up to respiratory arrest and death.	Euphoria, sense of well-being, stimulation, anxiety, increased energy, alteration in mood, floating feeling, dreamlike state, hallucinations, suicidal feelings, dependency.

* See page 4 for more information about serotonin syndrome

Brain chemistry: Tramadol consists of two chemical compounds whose molecular structures are mirror-images of each other. Both of these compounds contribute to its analgesic properties through different mechanisms that include both opioid and non-opioid (i.e. serotonergic and noradrenergic) components.

Tramadol and its main metabolite O-desmethyltramadol are agonists of the mu-opioid receptor, giving it its opioid analgesic effect. However, tramadol also acts both as a serotonin releaser and reuptake inhibitor and as a noradrenaline reuptake inhibitor, and these non-opioid components are thought to increase the analgesic effect.[1] This can be demonstrated in three ways: that naloxone only partially (approximately 30%) removes tramadol's painkilling effect, that administration of naloxone does not result in any significant withdrawal‡ and that pupils can become dilated rather than constricted after taking tramadol.[13]

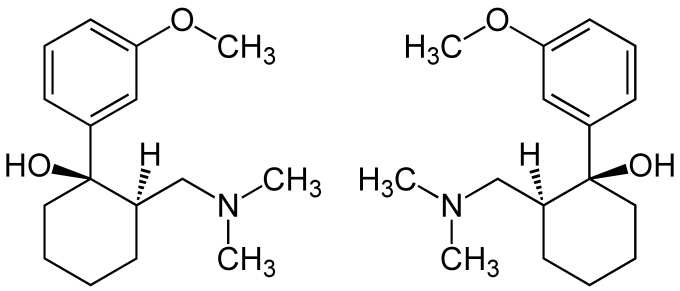

Fig. 3: (1R,2R)- & (1S,2S)-Tramadol Enantiomers Structural Formulae

In summary, tramadol's analgesic effect has not been fully understood, however it appears to be produced by a multi-modal mechanism involving the mu-opioid, serotonergic and noradrenergic systems. Its interaction with NMDA receptors may also play a part, both in terms of providing pain relief[14,15] and antidepressant effects.[16,17,18]

Patterns of use: While dependence on and abuse of tramadol can occur when used within its recommended dose range, these are more likely to occur when used above recommended doses. The extent of tramadol's potential to cause dependency is disputed, with some studies concluding that while it has a low potential for dependence its use over an extended period of time can lead to opioid-like physical dependence.[19] The majority of the cases of tramadol abuse are seen in people with a previous history of substance use;[20,21] withdrawal symptoms include restlessness, agitation, anxiety, sweating, insomnia and other symptoms similar to opioid withdrawal.[22,23]

‡ See page 5 for more information about the use of naloxone in tramadol overdose

Toxicity: Compared to morphine, tramadol is considered to be a relatively safe analgesic: fatal intoxications are rare and appear to be associated with overdoses of tramadol taken with other drugs (including alcohol).[3,24,25,26]

In the Republic of Ireland in 2013 there were 26 deaths where tramadol was mentioned in death certificates;[28] in Northern Ireland in 2015 there were 28 deaths[27] and in England and Wales this number was 240 in 2014, decreasing to 208 in 2015 and 184 in 2016.[29,30] Tramadol was the most commonly mentioned opioid drug in Northern Ireland in the 2015 UK Drug Situation report and was referred to in 19% of all drug related deaths.[29]

Age, gender and mental health also appear to play a part: in England and Wales in 2013 tramadol deaths showed an older age profile than most drug misuse deaths. Women were over-represented: 39% compared to 27% overall, with 18% of drug misuse deaths among women involving tramadol compared to 10% of men. An audit of tramadol overdose admissions to emergency departments in Wales in 2014 found that 85% of the patients were female.[31] A higher proportion of tramadol deaths in 2013 were suicides compared to drug misuse deaths (37% vs. 20%) and suicides accounted for half of tramadol-only deaths (48%).[32]

Seizures can occur at therapeutic doses but are mainly associated with doses above 400mg per day.[33,34,35] The incidence and severity of adverse effects depends on the dose, formulation and route of administration, with less adverse effects noted in slow-release preparations.[36]

Tramadol's actions on the serotonergic and noradrenergic systems have been shown to enhance insulin effects and promote glucose utilisation[37,38] which could result in decreased blood glucose concentrations. Individual case reports have highlighted severe hypoglycaemia as a possible consequence of tramadol overdose[38] which have been confirmed in case-controlled studies.[39,40]

Serotonin syndrome: When combined with serotonergic agents (for example SSRIs such as fluoxetine and citalopram, and MAOIs) tramadol may induce serotonin syndrome[5,41,42,43] which can be fatal if not recognised and dealt with both quickly and effectively. Symptoms include overheating, over-responsive reflexes, involuntary muscular contractions and relaxations, high blood pressure, mental distress and dilated pupils. Due to muscle tension being triggered by the condition, there is a potential of developing muscle tissue breakdown which can cause severe kidney damage and can be fatal. It is therefore dangerous to restrain individuals as increased agitation will lead to increased muscle tension if trying to break free from restraints.

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Treatment can include cooled IV fluids, benzodiazepines to control agitation, rapid cooling via ice packs, oral cyproheptadine (anti-histamine with anti-serotonergenic properties) and anti-psychotic medication in severe cases. Perceptual effects of serotonin toxicity can last up to 24 hours; there is also the possibility of 'rebound effects' more than 12 hours after initial symptoms.

Harm reduction advice: If you choose to use tramadol, taking some simple steps can reduce some of the risks and help you stay safer:

- **Stay within recommended doses**. The majority of serious side-effects from tramadol occur when using more than the recommended daily dosage. However, tramadol overdose can occur even from taking smaller doses, often in combination with other drugs.
- **Don't use alone**. Serious side effects such as seizures and low blood sugar can occur in certain people. Try to ensure that other people are with you when using tramadol, especially if it's your first time using.
- **Avoid mixing drugs.** Try to avoid mixing tramadol with other drugs, including prescription medication. Fatal overdose on tramadol alone is possible but is much more common when tramadol is mixed with other drugs, especially other central nervous system depressants. Mixing tramadol with prescribed medications can also lead to a range of dangerous and life-threatening conditions.
- **Avoid injecting tablets and capsules.** Injecting this form of tramadol whether IV, IM or subcutaneous risks overdose and death, and the fillers and binders in tramadol tablets when injected can cause local tissue necrosis, infection, pulmonary granulomas and increased risk of endocarditis and valvular heart injury.

Naloxone: While administration of naloxone may help to reverse some of the effects of an overdose of tramadol there is controversy around its use, particularly in relation to seizures. Some studies find that naloxone reduces the incidence of seizures in tramadol overdose,[44] while others report that low doses of naloxone could increase the risk of seizure.[45] Possibly due to tramadol's serotonergic and noradrenergic action, naloxone can be seen to have an inconsistent response in the event of tramadol overdose and while the findings do not suggest that naloxone should be withheld, the potential for seizure should be noted and any forthcoming seizure dealt with.[46]

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Recovery Position: The recovery position is for someone who is unconscious but breathing normally. If they are not breathing normally CPR is required, with an emphasis on giving supplementary oxygen via rescue breaths.

Start by placing their arm as if they are waving.

Place the other arm across their chest and hold their hand against their cheek.

Lift up the knee that is furthest from you. Continue to hold their hand in place.

Turn them on their side by pulling the knee towards you and down.

For further information on Overdose & Emergencies see UK and Ireland DrugWatch Information Sheet.

Where to get help: We would advise anyone experiencing issues from tramadol or other substances to seek medical support via their GP or the NHS. There are a wide range of local drug services throughout the UK, to find out what is available in your area please use the links below:

England: Find Support | Frank Scotland: Scottish Drug Services
Wales: Dan 24/7 Northern Ireland: Public Health Agency ROI: Drugs.IE

For further advice, medical professionals can use the National Poisons Information Service 24-hour telephone service on 0344 892 0111 or its online database, TOXBASE. Any health professional encountering an unusual or unexpected adverse reaction to the use of tramadol (or any other drug) should report the reaction to RIDR.

Written by Mark Adley in association with UK and Ireland DrugWatch: an informal online professional information network established by a group of professionals working in the UK and Irish drugs sector. The aim of the group is to raise/establish standards for drug information, alerts and warnings. It is currently an unfunded, bottom-up initiative that works in the spirit of mutual co-operation. Details of current members can be found here.

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Images

Fig. 1 Tramadol capsule by MRA

Fig. 2 Tramadol packaging by MRA

Fig. 3 Tramadol structural formulae by Wikimandia (own work) via Wikimedia Commons. Available online https://commons.wikimedia.org/wiki/File:(1R,2R)-%26_(1S,2S)-Tramadol_Enantiomers_Structural_Formulae.svg (accessed 26/11/2017).

Recovery position illustrations by Michael Linnell for Linnell Publications