

Tramadol

Update Review Report

Agenda item 6.1

Expert Committee on Drug Dependence
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Summary

Tramadol is a centrally acting analgesic with a multimode of action. It acts on serotonergic and noradrenergic nociception, while its metabolite O-desmethyltramadol acts on the μ -opioid receptor. Its analgesic potency is claimed to be about one tenth that of morphine. Tramadol is used to treat both acute and chronic pain of moderate to (moderately) severe intensity. Tramadol monotherapy does not usually provide adequate analgesia. In chronic non-cancer pain, there is little evidence for the use of tramadol for more than three months.

Tramadol is considered to be a relatively safe analgesic. The main adverse reactions to tramadol therapy are nausea, dizziness, and vomiting, particularly at the start of the therapy. At therapeutic doses, tramadol does not cause clinically relevant respiratory depression. Tramadol is contra-indicated, however, in patients with diminished respiratory function.

Tramadol is generally considered as a medicinal drug with a low potential for dependence relative to morphine. Nevertheless, tramadol dependence may occur when used for prolonged periods of time (more than several weeks to months). Dependence to tramadol may occur when used within the recommended dose range of tramadol but especially when used at supra-therapeutic doses. In many individuals with tramadol dependence, a substance abuse history is found.

Orally administered tramadol can produce opioid-like effects (both mentally and physically) but these effects are mild and not produced following parenteral administration. Tramadol is generally considered as a medicine with a low abuse potential relative to morphine, and this potential is associated with high dose oral tramadol.

At supra-therapeutic doses and rarely at therapeutic doses, intoxications may occur. Symptoms of tramadol intoxication are similar to those of other opioid analgesics but may include serotonergic and noradrenergic components. Symptoms include central nervous system (CNS) depression and coma, tachycardia, cardiovascular collapse, seizures, and respiratory depression up to respiratory arrest. Fatal intoxications are rare and appear to be associated with large overdoses of tramadol and co-ingestion of other drugs (including alcohol).

Tramadol is used worldwide and is listed in many medical guidelines for pain treatment. It is mentioned as a step-2 analgesic in the WHO guidelines for cancer pain relief. Tramadol is also listed on several national essential medicines lists. It is, however, not listed on the WHO Model List of Essential Medicines (April 2013).

There is growing evidence of abuse of tramadol in some African and West Asian countries considering large seizures of such preparations in North and West Africa. Abuse of tramadol is reported by Egypt, Gaza, Jordan, Lebanon, Libya, Mauritius, Saudi Arabia and Togo. Because of increasing rate of abuse, Egypt has up-scheduled tramadol in 2009.

Tramadol is widely available via the Internet without a prescription. Websites provide many user reports on the non-medicinal use of tramadol.

Legal status of tramadol differs internationally. In most countries, it is a prescription-only medicine.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Tramadol

B. *Chemical Abstract Service (CAS) Registry Number*

27203-92-5 (base)

36282-47-0 (hydrochloride salt)

22204-88-2 (hydrochloride salt)

C. *Other Names*

(±)-*cis*-(2-dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol

D. *Trade Names (hydrochloride salt; including combinational medicinal products)*

Acema, Actidol, Acty, Acugesic, Adamon, Admadol, Adolonta, Altadol, Amadol, Amanda, Amdol, Ammitran, An-Tian, Ana-Q, Anadol, Analab, Analtram, Anangor, Anatram, Andalpa, Arodol, Arrestadol, Astradol, Atdol, Avdol, Axidol, Axytram, Bei Pin, Bestodol, Bing Ning, Biodalgic, Biodil, Biodol, Biomadol, Biotram, Biotrama, Biotrany, Boldol, Bolodol, Bramadol, By-madiol, Cadol, Calmador, Calmpain, Camadol, Cambidol, Camigesik, Cemadol, Centrasic, Ceparidin, CG-MAC, Cincro Plus, Citra, Cloq, Combtram, Contradoc, Contram, Contramal, Conzip, Cormadol, Corsadol, Cortram, Cosdol, Crispin, Cromatodol, Cruzac, Cuntrol, D.M.Dol, Da Ma Err, Damadol, Damed, Damol, Darol, Didol, Doctramado, Dolan, Dolana, Dolbest, Dolbis, Dolfi, Dolfre, Dolga, Dolgesik, Dolma, Dolmal, Dolmax, Dolmeri, Dolocap, Dolocet, Dolodol, Dolol, Dolomed, Dolonil, Doloran, Dolotral, Dolotram, Dolotramin, Dolotramine, Dolpain, Dolpar, Dolpaz, Dols, Dolsic, Dolstar, Dolta, Doltel, Dolwin, Dolzam, Domadol, Dorless, Drobit, Dromadol, Durodor, Durotram, E-Dol, Ecodolor, Eltram, Esgipyrim, Etigesic, Eufindol, Fada Tramadol, Febrex, Feng Tong Ding, Forgesic, Formador, Fortradol, Fraxidol, FS, Gelotradol, Gemadol, GenRX Tramadol, Getpar, Glimadol, Gudil, Haldotram, Haledol, Hetradol, Hua Jie Wei, Hua Qu, Hyperdol, Idol, Imadol, Indolpara, Ingesic Forte, Inodol, Iodol, Ivydol, Ixprim, Jetra, Jpdol, K-Alma, Kamadol, Katrasic, Kdol-P, Kedol, Kevtram, Kontram, Lanalget, Le Shi Pu Kang, Leedol, Lexidol, Lucidol, Lumidol, M-Dol, Mabron, Madol, Madola, Mandolgin, Manol, Mapdol-P, Marodol, Medol, Meradol, Meridol, Metazac, Metracop, Microdol, Milador, Minidol, Mipro, Mobyia, Monoalgic, Monocrixo, Muaction, Nettram, Neutram, Nictram, Noax, Nobligan, Nomal, Nonalges, Nopidol, Notil, Novadol, Nufapotram, Nycodol, OC-Dol, Odel, Omodel, Ondol, OPI-OT, Opidol, Opigesic, Orasic, Oratram, Orchidol, Orozumadol, Osdol, Osmadol, Ospidol, Oxxalga, Ozitram, Pacmadol, Painadol, Painsol, Paine, Painlax, Paratel-P, Patradol, Patral, Paxilfar, Paxmax, Pengesic, Penover, Pinorec, Plazadol, Poltram, Postadol, Predalgic, Prontalgin, Prontofort, Protradon, PTR, Qi Zhi, Qimaite, Qu Feng, Qu Ming, Qu Teng, Qu Tong Kang, Qutong, Racetram, Rajdol, Ralgen, Ralivia, Ramadol, Ramax, Redimol, Relidol, Ridil, Rofy, Rotamol, Rui Li Ping, Rybix, Ryzolt, Sayadol, Sefmal, Seminac, Sensitram, Servodol, Siatram, Sigmadol, Simatral, Simudol, Sintradon, Slovadol, Souladol, Soztram, Splint Forte, Sridol, Stemadol, Strom,

Supridol, Surgidol, Sylador, T Dol, T-Long, Tacil, Tanadol, Tadol, Tai Mei Ding, Takadol, Takol, Talnex, Tamadol, Tamolan, Tamriv, Tamvrin, Taridol, Taxidol, Taz, TDL, TDX, Tecsadol, Temadol, Tendia, Teramadol, Theradol, Ti Ma Er, Tial, Timarol, Timasen, Tinlol, Tioner, Tiparol, Tlusic, TM-Plus, TMD, Tofdol, Tol-A, Tolma, Tong Ting, Topalgic, Toptra, Trabar, Trabilin, Trace, Traceta, Tracin-P, Tracine, Tractadol, Tradef, Tradol, Tradolan, Tradolgesic, Tradolor, Tradonal, Tradorec, Tradosik, Tradyl, Trafflash, Tragesic, Tragesik, Trail, Trak, Tral-ac, Tralenil, Tralgiol, Tralgit, Tralic, Tralodie, Tram-Proxyvon, Trama, Tramabene, Tramabeta, Tramabit, Tramacalm, Tramacap, Tramacet, Tramache, Tramacip, Tramacon, Tramaconti, Tramactil Uno, Tramacur, Tramacure, Tramada, Tramader, Tramadex, Tramadin, Tramadis, Tramadoc, Tramadol, Tramadol, Tramadolo, Tramadolor, Tramadon, Tramadura, Tramaflam, Tramaflash, Tramaforte, Tramag, Tramagem, Tramagesic, Tramagetic, Tramagit, Tramahexal, Tramake, Tramakind, Tramaklosidol, Tramal, Tramalan, Tramalek, Tramalex, Tramalgic, Tramalgin, Tramalin, Tramamed, Tramamerck, Tramanil, Tramapine, Tramared, Tramasindol, Tramasol, Tramaspen, Tramastad, Tramatas, Tramataur, Tramatyrol, Tramazac, Trambax, Trambo, tramcod, Tramcontin, Tramdop, Tramed, Tramedif, Tramedo, Tramedphano, Tramelene, Tramest, Tramex, Tramgesic, Trami, Tramico, Tramisol, Tramium, Tramjet, Tramned, Tramnom, Tramo, Tramoda, Tramodin, Tramoflex, Tramol, Tramolin, Tramospas, Tramrot, Tramp, Tramplas, Tramquel, Tramrod, Tramsars, Tramtor, Tramundal, Tramundin, Tramy, Tranal, Tranat, Trandol, Trandy, Transic, Trany, Tranzen, Trapain, Trapalin, Trapsure, Trasedal, Trasic, Trasik, Travex, Travictol, Trawel, Traxdol, Trazac, Trazodec, TRD, Treat, Tremolo, Tremtec, Trexol, Tridol, Tridural, Trodon, Trofel, Trol, Troma, Tromar, Tromy, Tropidol, Trosic, Trugesic, Trumac, Trump, Trunal, Trydol, Tryme, Tussdol, Ubitdol, Ultracon, Ultram, Ultramex, Unidol, Unitrama, Unitramarim, Urgendol, Utramal, Vardol, Veeradol, Vegadol, Veldrol, Verdol, Vertram, Victadol, Winpain, Wintram, Woolmar, Xi Li Xi Meng, Xiang Yang, Xidol, Xtradol, Xtram, Xtrapel, Xymel, Yi Bang, Yi Nuo Xing, Yin Jia, Yu Tong, Zaledor, Zaldiar, Zamadol, Zamudol, Zentra, Zephanal, Zodol, Zotadol, Zumalgic, Zumatram, Zydol, Zytram

E. *Street Names*

No data found.

F. *Physical properties*

Tramadol hydrochloride salt is a white crystalline powder and has a bitter taste.

G. *WHO Review History*

Tramadol was pre-reviewed for the first time at the 28th meeting of the Committee in 1992. The Committee did not recommend critical review on the basis of its low abuse liability as indicated by human studies on its subjective effects and the absence of significant abuse. At the 32nd meeting in 2000, tramadol was again pre-reviewed. The Committee noted significant numbers of cases of withdrawal syndrome and dependence reported as adverse drug reactions, as well as its potential to produce dependence of the morphine type, and recommended critical review of tramadol. At its 33rd meeting in 2002, the Committee decided that the information was not sufficient to recommend

international control of tramadol, but was adequate to recommend that WHO keep the drug under surveillance. Subsequently, tramadol was pre-reviewed at the 34th meeting in 2006. Considering that tramadol continued to show a low level of abuse, even following the major increase in the extent of its therapeutic use, the Committee concluded that there was not sufficient evidence to justify a critical review.

2. Chemistry

A. Chemical Name

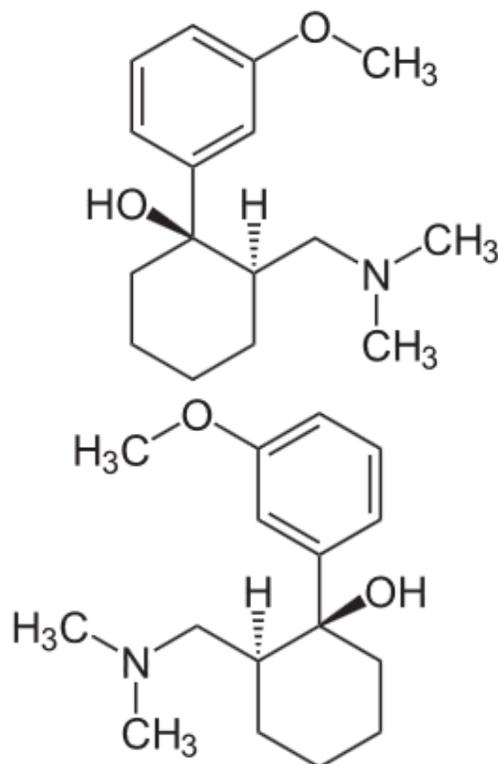
(1*S*,2*R*)-2-(dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexanol
or
(1*S*,2*R*)-2-(dimethylaminomethyl)-1-(*m*-methoxyphenyl)cyclohexanol

IUPAC Name: tramadol

CA Index Name: tramadol

B. Chemical Structure

Free base: *cis*-configuration



(1*S*,2*S*)-tramadol

(1*R*,2*R*)-tramadol

Molecular Formula:	C ₁₆ H ₂₅ NO ₂
Molecular Weight:	263.4 (base); 299.8 (hydrochloride salt)
Melting point:	hydrochloride salt: 180-181 °C
Boiling point:	
Fusion point:	

C. Stereoisomers

Tramadol has two chiral centres in the cyclohexane ring. Consequently, four different stereoisomers exist: (1R,2R), (1S,2S), (1R,2S), and the (1S,2R) stereoisomer.

The commercially available product contains the racemic (1:1) mixture of the (1R,2R) and the (1S,2S) enantiomers, also designated as the (+) and the (-) enantiomer of *cis*-(2-dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexanol, respectively. The (1R,2R) and (1S,2S) enantiomers have the hydroxyl and dimethylaminomethyl group in *cis*-configuration⁵⁵, and the methoxyphenyl group and the dimethylaminomethyl group in *trans*-configuration.

D. Synthesis

Tramadol was first synthesized in 1962 by Grünenthal GmbH in Germany by coupling of the corresponding cyclohexanon with 3-methoxyphenylmagnesium bromide in a Grignard reaction.^{20;21} More recently, the chemical synthesis of tramadol and two of its metabolites has been described by the same coupling reaction using organolithium derivatives.⁵

E. Chemical description

Tramadol shows structural resemblance with codeine. Both tramadol and codeine have a 3-methoxy group on the phenyl ring and share O-demethylation as a metabolic step, yielding metabolites with stronger μ -opioid agonist activity than the parent compound.

In addition, the dimethylaminomethyl moiety of tramadol resembles the methylated ring nitrogen of morphine and codeine, and forms an essential part of the pharmacophore that interacts with the μ -opioid receptor and monoamine transporters. N-demethylation yields metabolites that lack significant analgesic activity.^{43;82}

F. Chemical properties

Tramadol hydrochloride is readily soluble in water and methanol. It has a pK_a value of 9.41. The log partition coefficient (logP) in *n*-octanol-water is 1.35 at pH 7.

G. Chemical identification

Tramadol may be identified chemically by infrared spectroscopy, mass spectrometry, and nuclear magnetic resonance.⁹⁹ Many analytical methods for the identification and quantification of tramadol and major metabolites in body fluids have been described in the literature (see Baselt 2011¹² and Smyj et al 2013⁹⁹). Gas and liquid chromatographic techniques are available.

The enantiomeric separation of tramadol and metabolites by chiral chromatography has also been described.^{6;16}

Most commercial opioid immunoassays do not significantly cross-react with tramadol or its metabolites and do not detect tramadol.

3. Ease of convertibility into controlled substances

Based on its chemical structure, it is not likely that tramadol can be converted into a controlled substance.

4. General pharmacology

4.1. Pharmacodynamics

Tramadol exists as the racemic (1:1) mixture of the (+) and (-)-enantiomer. It has a multimodal mechanism of action as on the one hand the (+) and (-)-enantiomer act on the serotonin and noradrenaline reuptake, and on the other hand the O-desmethyl metabolite of tramadol (called M1 or ODT) acts on the μ -opioid receptor. This implies that the analgesic mechanism of action of tramadol includes both non-opioid components, i.e., noradrenergic and serotonergic components, and opioid components.^{43;82;94} 1). The (+)-enantiomer of tramadol contributes to analgesia by inhibiting the reuptake of serotonin, the (-)-enantiomer by inhibiting the reuptake of noradrenaline, and the O-desmethyl metabolite by binding with relative high affinity (compared to tramadol) to the μ -opioid receptor (Table 1).

(\pm)-Tramadol binds with low affinity to the human μ -opioid receptor with an affinity constant (K_i) of 2.4 μ M.⁴² This affinity is approximately 4000-fold less than that of morphine ($K_i = 0.34$ nM). The affinity of tramadol for the δ - and κ -opioid receptors is even less (Table 1). The (\pm)-O-desmethyl metabolite (M1) of tramadol, on the other hand, shows about 400-fold higher affinity for the μ -opioid receptor ($K_i = 5.4$ nM) than the parent compound, but still with much lower affinity than morphine. The affinity of M1 for the μ -opioid receptor is due to the (R) (+)-enantiomer ($K_i = 3.4$ nM) and not the (S) (-)-enantiomer ($K_i = 240$ nM). The affinity of the (R) (+)-enantiomer of M1 is one-tenth that of morphine for the μ -opioid receptor, and about 700 times that of (\pm)-tramadol. The metabolite (\pm)-M5 also has a higher affinity than (\pm)-tramadol for the μ -opioid receptor ($K_i = 100$ nM). However, animal studies indicate that M5 does not cross the blood-brain barrier and does not contribute to the anti-nociceptive effect of tramadol. The metabolites M2, M3, and M4 of tramadol have negligible affinity for the human μ -opioid receptor.^{42;43}

Table 1. Affinity of tramadol and O-desmethyltramadol (M1) for opioid receptors and their inhibition of monoamine uptake. Reproduced from Raffa et al (1992, 1993)^{83,84} and Gillen et al (2000)⁴².

Drug	K _i (μmol/L)					
	opioid receptor affinity				uptake inhibition	
	μ (human)	μ (rat)	δ	κ	noradrenaline	serotonin
(±)-Tramadol	2.4	2.1	58	43	0.79	0.99
(+)-Tramadol		1.3	62	54	2.51	0.53
(-)-Tramadol		24.8	213	54	0.43	2.35
(±)-M1	0.0054					
(+)-M1	0.0034					
(-)-M1	0.24					
Morphine	0.00062	0.00034	0.092	0.57	inactive	inactive

Data refer to rat receptors or tissues, except for affinity data for the μ-opioid receptor which are from human and rat receptors.

In addition to its opioid activity, tramadol acts on serotonergic and noradrenergic pathways, which is thought to act synergistically with tramadol's effects on the μ-opioid receptor. The fact that non-opioid mechanisms are involved in the analgesic effect is supported by the observation that naloxone only partially (approx. 30%) antagonised tramadol-induced analgesia and that quinidine (an inhibitor of hepatic demethylation of tramadol into M1) inhibited tramadol-induced miosis but hardly affected tramadol analgesia.²⁶ In addition, Desmeules et al (1996) found that yohimbine (an α₂-adrenoceptor antagonist) was able to significantly reduce the analgesic effect of tramadol in healthy volunteers (maximum decrease 67% and 97% at 2.8 h, by subjective and objective measures, respectively).³² These data suggest significant agonist activity (i.e., of O-desmethyltramadol) at the μ-opioid receptor and the involvement of non-opioid mechanisms in tramadol analgesia.

Tramadol appears to act both as a serotonin releaser and as a serotonin reuptake inhibitor, and as a reuptake inhibitor of noradrenaline *in vitro*.⁴³ (+)-Tramadol is the enantiomer with highest activity as a serotonin releaser and reuptake inhibitor in rat dorsal raphe nucleus brain slices.⁸ The (+)-enantiomer is about four times more potent than the (-)-enantiomer as serotonin reuptake inhibitor.³³ Besides, tramadol is an effective blocker of noradrenaline reuptake in rat spinal cord synaptosomes by blocking the noradrenaline transporter.⁸⁶ As a noradrenaline reuptake inhibitor, (-)-tramadol is about ten times more potent than (+)-tramadol in rat hypothalamic synaptosomes.³³

Minami et al. (2007) reviewed the effects of tramadol on monoamine transporters and G-protein coupled receptors.⁷⁰ They concluded that G-protein coupled receptors and ligand-gated ion channels may also be targets for tramadol. It is, however, not known if the actions of tramadol on these receptors are involved in the analgesic effect of tramadol.⁷⁰

In summary, the analgesic effect of tramadol appears to be produced in a multimodal mechanism involving the μ-opioid system, the noradrenergic system, and the serotonergic system. Tramadol appears to act a releaser and reuptake inhibitor of

serotonin, and as a reuptake inhibitor of noradrenaline, and its metabolite is active as a μ -opioid receptor agonist. (+)-Tramadol is primarily responsible for serotonin reuptake inhibition, (-)-tramadol for noradrenaline reuptake inhibition, and the metabolite O-desmethyltramadol (M1) is primarily responsible for the agonist activity on the μ -opioid receptor.

Analgesia

Tramadol, a centrally acting analgesic, is used to treat moderate to (moderately) severe pain. Racemic tramadol provides similar analgesia as (+)-tramadol but is better tolerated than the (+)-enantiomer. In addition, the (-)-enantiomer is less effective as an analgesic. Therefore, the racemic mixture of tramadol is superior to either enantiomer alone in the treatment of pain.

As an analgesic, tramadol is approximately equipotent as codeine and has about 10% of the potency of morphine after parenteral administration. Because tramadol has a higher oral bioavailability than morphine, the relative potency of oral tramadol should be about 20% of that of oral morphine.⁴³ In humans, analgesia by tramadol is induced about one hour after oral administration and peaks after two to three hours. The analgesic effect is dose-dependent and due to both the parent drug and the O-desmethyl metabolite M1. The risk of respiratory depression is low compared to other opioids like morphine, pethidine, and oxycodone.^{43;81}

Tramadol has a wide range of applications in both acute (e.g., postoperative, trauma) and chronic (cancer and non-cancer) pain (see reviews^{10;43;54;59;94}). Nevertheless, recent meta-analyses show that tramadol monotherapy does not always provide sufficient analgesia. For example, tramadol showed no significant effect on pain relief in chronic nonspecific low back pain.²² In another meta-analysis, tramadol was found to be better than placebo in chronic low back pain, but the evidence was of low quality.¹⁹ In chronic osteoarthritis, meta-analyses show that the efficacy of tramadol is modest and that the evidence for efficacy is fair.^{18;62;67} Manchikanti et al. (2011)⁶² concluded that the evidence for tramadol in managing osteoarthritis (knee and multiple joints) was fair, and that the evidence was poor in all other conditions of chronic non-cancer pain. On the other hand, a meta-analysis carried out in 2006 showed efficacy of tramadol in the treatment of neuropathic pain.⁴⁶

In a recent review carried out by a German expert committee, the authors confirmed the analgesic efficacy of tramadol, with strong evidence from systematic reviews and (inter)national guidelines on acute and chronic pain management.⁸¹ The authors added that tramadol monotherapy does not usually provide sufficient analgesia in moderate to severe pain, and that German guidelines show that there is little evidence for the use of opioids, including tramadol, for more than three months in chronic non-cancer pain.⁸⁷

4.2. Routes of administration and dosage

Tramadol is marketed as the hydrochloride salt and is available in a variety of pharmaceutical formulations for oral (tablets, capsules), sublingual (drops), intranasal, rectal (suppositories), intravenous, subcutaneous, and intramuscular administration. It is also available in combination with acetaminophen (paracetamol). Immediate-release

and extended-release formulations are available. The following pharmaceutical formulations are available for oral use:

- 50 mg immediate-release tablets/capsules
- 50 mg; 100 mg; 150 mg; 200 mg; and 300 mg extended-release tablets/capsules
- 37.5 mg tramadol + 325 mg acetaminophen tablets/capsules

The recommended daily dose is in the range of 100-400 mg. The maximum dose should not exceed 400 mg per day. Normal-release forms may be given every 4-6 hours and the extended-release forms should be given every 12-24 hours. To minimise adverse effects at the start of the therapy and to improve tolerability, a 10-day or 16-day titration schedule of tramadol (immediate-release) is recommended.²⁷ Extended-release preparations are better tolerated and are dosed once or twice daily.

4.3. Pharmacokinetics

Pharmacokinetic data are mainly from the electronic Medicines Compendium (eMC) which contains Summaries of Product Characteristics (SPCs) checked and approved by the European Medicines Agency.³⁵

Absorption

Tramadol is almost completely absorbed after oral (>90%), rectal and intramuscular administration. Average bioavailability is 70%, irrespective of current food intake. Peak plasma concentrations after oral, rectal and intramuscular administration are reached in 1-2 hours, 3 hours, and 45 minutes, respectively. Extended-release preparations produce a smoother plasma concentration profile and have lower (about half) peak concentrations after 4 to 6 hours.^{35;54}

Peak plasma concentrations of tramadol after single dose oral administration (100 mg) are 0.31 ± 0.08 mg/L.³⁵ Peak plasma concentrations of O-desmethyltramadol usually are 15-25% those of tramadol.

The pharmacokinetics of oral and intravenous tramadol do not differ significantly between adults and children.

Distribution

The distribution volume of tramadol is about 2.6-2.9 L/kg bodyweight, following a 100-mg intravenous dose. Plasma protein binding is approximately 20%.

Metabolism and elimination

Tramadol is extensively metabolised in the liver by demethylation, oxidation and conjugation (sulphation and glucuronidation).³⁵ Twenty-three metabolites have been identified.¹¹⁸ Both O- and N-desmethyl metabolites are formed, including di- and tri-desmethyl derivatives. O-demethylation occurs primarily by the hepatic enzyme cytochrome P450 2D6 (CYP2D6) and N-demethylation by cytochrome P450 3A4 (CYP 3A4).^{4;10}

The O-demethylation reaction, yielding the active metabolite O-desmethyltramadol, depends on the activity of the enzyme CYP 2D6. This enzyme displays genetic polymorphism. Slow metabolisers have relatively low

plasma concentrations of O-desmethyltramadol, whereas (ultra)rapid metabolisers have relatively high plasma concentrations of this active metabolite. As such, CYP 2D6 activity affects tramadol's analgesic activity. CYP 2D6 can be inhibited by a number of medicines, including various antidepressants and oral contraceptives. Concomitant therapy with such inhibitors may affect the analgesic effect of tramadol.

Oral tramadol is eliminated in urine (90%) and the faeces (10%). About 30% of an oral dose is excreted unchanged in the urine, and about 60% in the form of free and conjugated metabolites.^{12;43}

The elimination half-life of racemic tramadol is approximately 6 hours, irrespective of the mode of administration, and about 8 hours for O-desmethyltramadol.¹² Half-lives may be prolonged in people with decreased liver or kidney function.³⁵

At therapeutic doses, tramadol shows linear pharmacokinetics. The analgesic effect is dose dependent and serum concentrations of 0.1-0.3 mg/L are considered effective.³⁵

5. Toxicology

Animal studies did not reveal a carcinogenic effect of tramadol. Reproductive and developmental toxicity studies were negative. In addition, mutagenicity studies did not show evidence of a genotoxic risk to man.⁶⁵

Compared to the classical opioid analgesic morphine, tramadol is considered to be a relatively safe analgesic. Few cases of fatal poisoning due to tramadol alone have been reported in the literature.^{9;30;31;61;71;72} More frequent are intoxications with co-ingestion of other drugs or alcohol.^{25;63;69;110} Symptoms following a tramadol intoxication are similar to those of other opioids analgesics. These include central nervous system (CNS) depression, including coma, nausea and vomiting, tachycardia, cardiovascular collapse, seizures, and respiratory depression up to respiratory arrest.³⁵ Moreover, in combination with serotonergic agents (in particular, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors) tramadol may induce the serotonin syndrome.^{35;47;52;56;58;73;90;107} The hyperthermia in the serotonin syndrome is potentially fatal.

Few cases of tramadol-related severe respiratory depression have been described in the literature. The cases described all concern cases of overdosing.^{89;102;112} Intravenous naloxone has been successfully used to reverse the opioid effects of tramadol overdose.^{64;89}

A male patient with acute respiratory distress syndrome had a blood concentration of 9.5 mg/L tramadol, without toxic levels of other drugs.¹¹² The patient presented with tachycardia, deep coma and bilaterally dilated pupils. He had mixed respiratory and metabolic acidosis, and needed mechanical ventilation. Subsequently, he developed multiple organ dysfunction and had seizures for two days.

A patient with pre-operative renal impairment developed a low respiratory rate (2-3/min) and narrow pupils after repeated administration of tramadol following renal

surgery.¹⁰² Peak plasma concentrations of (+)-tramadol, (-)-tramadol, (+)-O-desmethyltramadol and (-)-O-desmethyltramadol were 0.9 mg/L, 1 mg/L, 0.17 mg/L and 0.22 mg/L, respectively. Genotyping revealed that the patient was a CYP2D6 ultra-rapid metaboliser which – in conjunction with the renal impairment – may have resulted in lower renal clearance of the O-desmethyl metabolite.

In a case series of deliberate tramadol self-poisonings, 19 patients (3.6%) had apnoea and received respiratory support or naloxone.⁴⁵ The mean dose ingested by those experiencing apnoea (2125 ± 1360 mg; range 200-4600 mg) was significantly higher than the dose ingested by those who did not experience apnoea (1383 ± 1088 mg; range 100-6000 mg). This study has been rightly criticized by the lack of laboratory confirmation of tramadol-only poisoning.⁹¹

Electrocardiographic changes after tramadol overdoses may include QRS prolongation, non-specific ST-segment and T-wave changes, first-degree atrioventricular block, atrial fibrillation, prolonged corrected QT intervals, and ventricular dysrhythmias. Rarely, cardiopulmonary arrest has occurred after tramadol overdose.^{29;31;63;97} Refractory circulatory shock has been described in an CYP2D6 ultra-rapid metaboliser, admitting tramadol consumption to gain a 'high' sensation³⁶, but in view of the tramadol dose taken (4.5 gram) the relevance of the patient's metaboliser status must be questioned.

These case histories show that fatal or near-fatal intoxications are associated with supra-therapeutic doses (overdoses) of tramadol and that intoxications at therapeutic doses are rare.

Rarely, seizures occur at therapeutic doses of tramadol. Seizures appear to be mainly associated with doses exceeding the maximum recommended dose of 400 mg per day.^{3;13;39;53;64;103;104;107} Seizure risks of up till 54% of cases (overdose or abuse) have been found and in some studies the risk was related to the dose of tramadol ingested. Recurrent seizures are not common and the usual outcome is full recovery.⁹⁶ ECG parameters were not predictive for seizures.³⁷ Symptoms of seizures after tramadol ingestion have also been reported in infants.⁶⁶

In a retrospective chart review of tramadol exposures reported to the California Poison Control System (N = 190; co-ingestant cases excluded; study period January 1999 to July 2001), seizures ranked fourth in observed adverse effects.⁶⁴ Main symptoms were CNS depression (27%), nausea and vomiting (21%), tachycardia (17%), and seizures (13.7%). Ingested doses ranged from a few milligrams to 5000 mg. The lowest dose associated with seizures was 200 mg and 85% of seizures developed within 6 hours of tramadol ingestion. Of the 26 patients with seizures, 81% had one seizure, 3.8% had two seizures, and 11.5% had multiple seizures. No patient developed status epilepticus. Seven out of 8 patients with documented data responded to naloxone with improved mental status. One patient had severe respiratory depression. Serious toxicity from tramadol exposures was rare.

In a surveillance study in the USA, seizure risk was associated with age 24-54 years, with more than four tramadol prescriptions, and with a history of alcohol abuse, stroke or head injury.⁴¹

Seizures induced by high doses of tramadol has been observed in rodents and appeared to be comparable with the potential of codeine to induce seizures.⁸⁵ (+)-Tramadol and

(-)-tramadol were about equipotent in this respect, whereas metabolites, including (+)-M1 and (-)-M1, were less potent than tramadol.

6. Adverse reactions in humans

Adverse reactions of therapeutic use of tramadol include nausea and dizziness (> 10%), drowsiness, fatigue, headache, increased sweating, vomiting, dry mouth, constipation (1-10%), diarrhoea, and cardiovascular dysregulation (palpitations, tachycardia, postural hypotension - particularly after rapid intravenous administration) (0.1-1%). Respiratory depression, epileptiform convulsions, tremor, bradycardia, hallucinations, and anxiety are rare (0.01-0.1%).^{35;51}

Dependence to tramadol may occur.^{35;100;114;122} Withdrawal reactions include restlessness, agitation, anxiety, sweating, insomnia, hyperkinesia, tremor, paresthesias, and gastrointestinal symptoms, similar to opioid withdrawal symptoms.^{11;40;77}

The incidence of adverse effects depends on the dose and the mode of administration.^{10;43} Sustained-release preparations show a better tolerability profile.⁵⁴

Analysis of French pharmacovigilance data from the period 1987-2006 indicated that the incidence of adverse reactions to the tramadol-paracetamol combination was 44.5 cases per 10⁵ patient-years, which was significantly higher than for the dextropropoxyphene-paracetamol combination (24.9) and the codeine-paracetamol combination (12.5).¹⁰⁸ The relatively short pharmacovigilance period of the tramadol-paracetamol combination (introduced in France in 2002) compared to the two other combinations (introduced in 1970 and 1985, respectively) may have biased the results.

Effects on respiration

Opiates reduce the sensitivity of the respiratory centre to carbon dioxide. This may result in decreased tidal volume and decreased respiratory rate. Because of the μ -opioid agonist activity of O-desmethyltramadol, tramadol may lower the respiratory rate and potentially lead to severe respiratory depression. This has incidentally been observed in overdose cases of tramadol.^{89;102;112} However, at therapeutic doses tramadol is not likely to cause significant respiratory depression.⁴³

In healthy subjects, tramadol reduced the sensitivity to carbon dioxide, but did not reduce the ventilatory response to hypoxia.¹¹³ At therapeutic doses, tramadol produced less respiratory depression, both in adults and in children, compared to morphine, pethidine, and oxycodone.^{14;48;105;106;111} In neonates undergoing surgery in Benin City (Nigeria), tramadol provided adequate analgesia without significant complications.⁷⁸ Nevertheless, in patients at risk for respiratory depression, the use of tramadol is contra-indicated.³⁵

7. Dependence potential

Animal studies showed that physical dependence on tramadol may develop, but this is not consistently seen in all studies. In rhesus monkeys, only mild to moderate withdrawal symptoms were detected (see review³⁸).

Human data also indicated that tramadol produces opioid-like effects after oral administration, but not after parenteral administration. The evidence for physical dependence was considered minimal. Withdrawal symptoms appear to be mild and partially resemble those seen after cessation of the use of serotonin-specific reuptake inhibitors (SSRIs) (see review³⁸). Consequently, tramadol is generally considered as a drug with low potential for dependence. In the last few years, new data have been reported and these data confirm that tramadol dependence may occur when used daily for more than a few weeks/months.

In many cases of tramadol dependence, a history of substance abuse is present.^{92;109} However, dependence does also occur in individuals without substance abuse history.^{98;100} In dependent opioid abusers, tramadol acts as a mild opioid agonist able to suppress opioid withdrawal symptoms, though statistically not to a significant degree, comparable to hydromorphone.¹⁷ In this study of Carroll et al (2006), tramadol did not show opioid antagonist effects. In another study among 6 opioid-dependent subjects on methadone maintenance therapy, intramuscular tramadol (100 and 300 mg) did not produce agonist activity (opioid-like effects) nor antagonist activity (withdrawal symptoms).¹⁵

In prescription-opioid users with opioid dependence, extended-release tramadol 200 mg modestly attenuated withdrawal symptoms, whereas the 600 mg extended-release preparation was ineffective and caused more use of breakthrough withdrawal medication.⁶⁰ In the second part of this study, cessation of the 600 mg extended-release tramadol preparation (treatment for one week) produced mild opioid withdrawal symptoms.

Occasionally, withdrawal symptoms of tramadol dependence have been treated effectively with buprenorphine-naloxone.⁸⁸

Zhang et al (2013) studied tramadol dependence in users without a history of substance abuse.¹²¹ According to the authors, tramadol has been a drug of abuse ever since its introduction in China as a non-controlled analgesic medicine. After placing under national control in 2007, tramadol use among drug abusers declined from 13.3% in 2009 to 3.4% in 2011. However, it remained relatively high in some regions. Therefore, the authors started a study to characterise tramadol-dependent users spontaneously visiting the addiction unit (Medical Hospital, Guangzhou, China) from July 2012 till January 2013. Twenty-three tramadol dependent users were identified in the study period. The median dose was not clearly defined (described as from 750 mg per time to 2000 mg per time, with a dose range from 100 mg to 10,000 mg). Prescription data in the general population were not given and the prevalence of tramadol dependence cannot be derived from this study. Therefore, the author's conclusion that tramadol has a high risk of producing dependence is not substantiated.

In a recent German study (including a literature study, an analysis of two drug safety databases, and questionnaires analyses), the low abuse and low dependence potential of tramadol were re-confirmed.⁸¹ From these two databases, the incidence of abuse or dependence was calculated as 0.12 and 0.21 per million defined daily doses (300 mg tramadol), respectively. The German expert group found a low prevalence of abuse or dependence in clinical practice in Germany, and concluded that tramadol has a low potential for misuse, abuse, and dependence in Germany.⁸¹

Analysis of the data from the Swedish pharmacovigilance system (spontaneous reports) identified 104 cases of tramadol dependence (fulfilling DSM-IV criteria) out of 550 tramadol-related reports of adverse drug reactions during the study period (1995 to 2006).¹⁰⁹ This number of 104 cases corresponded to 0.48 cases per million DDDs. Thirty percent of these cases had a documented history of substance abuse and 39% had a documented history of illicit drug use in the last 10 years. Hospitalisation was reported in 50% of the cases, mostly in a psychiatric or dependence clinic.

Withdrawal intensity has recently been studied in a group of opioid-dependent adults who were maintained on two different daily oral doses of tramadol (200 mg/day and 800 mg/day, respectively) during a 4-week study period.⁵⁷ Acute withdrawal effects were tested after intramuscular placebo, naloxone, or hydromorphone. Naloxone caused withdrawal symptoms. The intensity of these symptoms was positively related to both naloxone challenge dose and tramadol maintenance dose. Magnitude of naloxone-induced antagonistic effects during 800 mg/day tramadol maintenance was similar to the magnitude of naloxone antagonism during 60 mg (15 mg q.i.d.) subcutaneous morphine maintenance. Intramuscular hydromorphone challenge produced opioid-agonistic effects that were not attenuated by either tramadol maintenance therapy. The results show that chronic tramadol administration can produce dose-related opioid-like physical dependence in opioid-dependent adults.⁵⁷

In summary, the data on the dependence potential of tramadol show that tramadol has a relatively low dependence potential and that dependence is associated with the use of tramadol over an extended period of time (more than a few weeks to months). The data also show a higher risk profile in former drug abusers and in medical staff personnel than in pain patients. Several studies indicate that the incidence of tramadol dependence may differ between countries and within different regions of countries, which may be associated with the availability and prescription practice for tramadol, and with the availability of alternative psychoactive substances for drug abusers.

8. Abuse potential

Based on animal studies, tramadol is an atypical opioid analgesic with mild opioid-like effects (see review³⁸). Based on self-administration in monkeys, tramadol has some abuse potential but less so than morphine. This has recently been confirmed in a rat model of self-administration under a fixed-ratio and progressive-ratio schedule. In this study, tramadol acted as a weak reinforcer of self-administration compared to remifentanyl and morphine.⁷⁵

Human studies show that tramadol has a low abuse potential relative to the prototypic opioid morphine (see review³⁸). Opioid-like effects can be produced by oral administration of tramadol, but these are mild and not produced by parenteral administration.³⁸ In agreement with this, volunteer non-dependent opiate abusers ('post-addicts') were able to identify 300 mg tramadol, but not 75 mg and 100 mg, as an opioid-like substance when administered intramuscularly. This dose of 300 mg tramadol did not produce significant liking scores, miosis, or other morphine-like effects.⁷⁹

A recent study in humans has confirmed the opioid activity of oral tramadol.³⁴ Non-dependent subjects (n=8) were trained to discriminate between placebo, hydromorphone (8 mg) and methylphenidate (60 mg). In the following drug discrimination sessions,

subjects were able to identify orally administered tramadol as an opioid drug. Lower doses of tramadol (50 mg and 100 mg) were generally identified as placebo, whereas 200 mg and 400 mg tramadol were identified as hydromorphone or opioid-like. The 400 mg dose of tramadol did not significantly increase ratings of drug liking and ‘good’ effects, but did increase the scores on the stimulant scale. Such a profile fits with tramadol’s dual mechanism of action, i.e., its activity at the monoaminergic system and the activity of tramadol’s metabolite M1 at the μ -opioid receptor. The authors concluded that this effect profile of tramadol is consistent with a modest abuse liability for tramadol.³⁴ This effect profile is well explained by the gradual formation of the metabolite (M1) that is active at the μ -opioid receptor.

In contrast, oral tramadol appeared to act as a reinforcer in non-dependent opioid abusers, comparable to oxycodone.⁷ In this laboratory study with 9 participants, both the 200 mg and the 400 mg tramadol dose increased ‘like drug’ effect and decreased pupil size, relative to placebo, and all subjects identified 400 mg tramadol as an opioid agonist on the Drug Identification Questionnaire. The time-to-peak effect for miosis was substantially later for tramadol (i.e., 4 h) than for oxycodone or codeine (i.e., 1–2.4 h). Next to this effect, tramadol functioned as a reinforcer as the 400-mg dose was readily self-administered. The 200-mg dose failed to significantly increase self-administration, which shows that self-administration of tramadol is dose dependent. The authors concluded that oral tramadol has reinforcing efficacy in non-dependent opioid abusers, confirming its abuse potential in this population.⁷

Also in recreational drug users (n=22), 100 mg oral tramadol was found to induce effects of ‘drug liking’ and ‘want to take again’.¹²⁰ The drug ratings were comparable to those of 25 mg morphine but lagged behind those of morphine in some subjects. These data indicate that tramadol has abuse liability in recreational drug users, too.

A history of drug abuse is frequently detected among tramadol abusers.^{24;109;119} Data indicate that there is a growing number of tramadol abusers, in particular in some Middle East countries.^{50;74;80;103} In a recent study, the association of tramadol use and use of other psychoactive substances was investigated in high school students (n=1894; response rate 95%) in Ilam city of Iran.⁷⁴ Life-time prevalence of tramadol misuse was 4.7% and lifetime tramadol misuse was associated with last month alcohol use, cannabis use, and ecstasy use. Adjusted odds ratios were 2.2 (CI: 1.1-4.4) for last-month alcohol use, 5.0 (CI: 1.5-21.6) for cannabis use, and 8.9 (CI: 2.7-29.4) for ecstasy. In an analysis of tramadol poisonings (n=401 from March 2008 to March 2009; 266 mild and excluded; 135 included in the study; confirmation by blood analyses) in Iran, the investigators found 70 cases of intentional intoxications and 40 cases of recreational abuse (euphoria intention).¹⁰³ A history of chronic tramadol abuse was found in 34 cases.

In the United States, tramadol was introduced in 1994 on the market as medicine to treat pain. Several post-marketing studies have been published since. Data of the first post-marketing surveillance program started shortly after the introduction of tramadol showed that the reported rate of tramadol abuse (rated as positive, possible and alleged) was 1-3 cases per 100,000 patients in the first three years (1995-1998).²³ The majority of abuse cases (97%) concerned individuals with a history of substance abuse. Analysis of the surveillance data over five years (1995 to 2000) indicated that nearly 40% of all adverse reactions were withdrawal symptoms associated with chronic tramadol use.⁹⁵ Most cases showed typical opiate withdrawal symptoms, but 12% of cases presented as

atypical (severe anxiety and panic attacks, paranoia, unusual sensory phenomena, and hallucinations). The incidence of withdrawal symptoms (both typical and atypical) was about 0.5-1 per 100,000 individuals in the period 1999-2000 following a peak that was observed in 1996, i.e., one year after its introduction in the United States. Reporting bias and non-representative sampling of cases may have underestimated the true incidence of abuse.⁶⁸

Further monitoring up to 2004 showed that the rates of abuse remained stable, despite the introduction of new brands and new generic formulations.²⁴ Again, this study confirmed that abuse was found almost exclusively (95%) in individuals with a history of substance abuse. This is consistent with the general view that therapeutic use of analgesics rarely leads to abuse in pain patients.

Using structured interviews (up to nine) over a 12-month period, the prevalence of tramadol abuse was also assessed in patients with chronic non-cancer pain in a prospective 3-arm study (11,352 subjects).¹ Patients with an active substance abuse problem were excluded from the study, but patients with a history of abuse were included. Abuse (expressed as at least once during the 12-month follow-up) occurred in 2.7% of patients receiving tramadol, in 2.5% of patients receiving NSAIDs, and in 4.9% of patients receiving hydrocodone. Using more than one-time abuse as criterion of persistence, the abuse rates were 0.7% for tramadol, 0.5% for NSAIDs, and 1.2% for hydrocodone.¹ The abuse rates for tramadol and NSAIDs were significantly less than the abuse rate for hydrocodone. These results show that the use of analgesics rarely leads to abuse in patients who use tramadol therapeutically to relieve pain and who have no active substance abuse problem.

The German expert group mentioned before studied the abuse and dependence potential of tramadol by analysis of animal and human studies, and of two drug safety databases (WHO Vigibase and originator's safety database). From these two databases, the incidence of abuse or dependence was calculated as 0.12 and 0.21 cases per million defined daily doses (300 mg tramadol), respectively. The expert group concluded that tramadol has a low potential for misuse, abuse, and dependence, and that abuse or dependence has a low prevalence in clinical practice in Germany.⁸¹

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Tramadol is used to treat moderate to severe pain (most countries) or moderate to moderately severe pain (USA). It has a wide range of applications in both acute (e.g., postoperative, trauma) and chronic (cancer and non-cancer) pain (see reviews^{10;43;54;59;81;94}), and is worldwide available as a medicine.

Tramadol is listed in many medical guidelines for pain treatment. It is mentioned as a step-2 analgesic in the WHO guidelines for cancer pain relief.¹¹⁵ In chronic non-cancer pain, tramadol may be appropriate when non-opioid analgesics are ineffective or contraindicated.

In general, the analgesic effect of tramadol monotherapy is modest. In meta-analyses, tramadol showed no significant effect on pain relief in chronic nonspecific low back pain²², some effect (low quality evidence) in chronic low back pain¹⁹, and a modest effect (fair evidence) in chronic osteoarthritis^{18;62;67} Manchikanti et al. (2011)⁶²

concluded that the evidence for tramadol in managing osteoarthritis (knee and multiple joints) was fair, and that the evidence was poor in all other conditions of chronic non-cancer pain. On the other hand, a meta-analysis carried out in 2006 showed efficacy of tramadol in the treatment of neuropathic pain.⁴⁶

In a review by a German expert committee, the authors re-confirmed the analgesic efficacy of tramadol with strong evidence from systematic reviews and (inter)national guidelines on acute and chronic pain management.⁸¹ The authors added that tramadol monotherapy does not usually provide sufficient analgesia and that there is little evidence from German medical guidelines for the use of opioids, including tramadol, for more than three months in chronic non-cancer pain (see German guidelines⁸⁷).

From the manufacturer's records on the total amount of tramadol used, the total amount of tramadol used worldwide in the period from 1990 to 2009 was calculated to be 11,758 million DDDs (1 DDD defined as 300 mg).⁸¹

In Germany, a shift has been observed from the use of immediate-release preparations to extended-release preparations in the period from 2000 to 2010.⁹³ Treatment with immediate-release tramadol fell from 2.14% in 2000 to 1.29% in 2010 (-39.6%). In the same period, treatment with extended-release tramadol rose by 103%. Extended-release preparations of tramadol yield lower peak blood concentrations of tramadol and its metabolite M1, and show a better tolerability profile.⁵⁴ Such a favourable effect of lower blood concentrations may also apply to the abuse and dependence potential of tramadol, which would be consistent with the low rate of abuse and dependence in Germany that has been reported by Radbruch et al (2013).⁸¹

10. Listing on the WHO Model List of Essential Medicines

Tramadol is not listed on the WHO Model List of Essential Medicines, 18th edition, 2013.¹¹⁶ However, it is listed in several national essential medicines lists (e.g., Bhutan, Botswana, several provinces of China, Congo, Cook Islands, Côte d'Ivoire, Croatia, Dominican Republic, Ecuador, Egypt, Ghana, Honduras, India, Iraq, Jamaica, Maldives, Montenegro, Morocco, Myanmar, Namibia, Peru, Philippines, Republic of Moldova, Rwanda, Serbia, Seychelles, Slovakia, Slovenia, Sri Lanka, Sudan, Tajikistan, Thailand, The former Yugoslav Republic of Macedonia, Timor-Leste, Togo, Trinidad and Tobago, United Republic of Tanzania, Uruguay).¹¹⁷

11. Marketing authorizations (as a medicine)

Marketing authorisations for tramadol as a medicine are held by many companies. Examples (not limited) are Winthrop Pharmaceuticals, Zentiva, Actavis, Consilient Health, Bristol Laboratories Ltd, BMM Pharma, Ethypharm SA, Sandoz Pharmaceutical, Nippon Shinyaku Co, Beacon Pharmaceuticals, Sanofi Aventis France, Actavis Elizabeth, Amneal Pharmaceuticals, Watson Labs, Caraco, Sandoz, Asta, Teva Pharma BV, Mylan Pharmaceuticals Inc, Apotex Inc, Pliva, Mallinckrodt, Mylan, Northstar Healthcare, Sun Pharma Global, Anchen Pharms, Lupin Ltd, IPCA Labs Ltd, Meda Pharma BV, Apotex Europe BV, Pharmachemie BV, Grünenthal GmbH, Gedeon Richter Plc, Janssen Pharmaceuticals.

12. Industrial use

Industrial use of tramadol is not reported.

13. Non-medical use, abuse and dependence

Tramadol is widely available via the Internet without a prescription. The website EROWID, and other websites as well, provide many user reports of the non-medicinal use of tramadol.

Data from the post-marketing surveillance program in the USA, started shortly after the introduction of tramadol, showed that the reported rate of tramadol abuse (rated as positive, possible and alleged) was 1-3 cases per 100,000 patients in the first three years (1995-1998).²³ Analysis of the surveillance data over five years (1995 to 2000) indicated that an incidence of withdrawal symptoms (both typical and atypical) of about 0.5-1 per 100,000 individuals in the period 1999-2000 following the peak in 1996, i.e., one year after its introduction in the United States.⁹⁵ Reporting bias and non-representative sampling of cases may have underestimated the true incidence of abuse.⁶⁸ Further monitoring up to 2004 showed that the rates of abuse remained stable, despite the introduction of new brands and new generic formulations.²⁴ This study confirmed that abuse was found almost exclusively (95%) in individuals with a history of substance abuse. This is consistent with the general view that therapeutic use of analgesics rarely leads to abuse in pain patients.

In Iran, tramadol was approved as an analgesic in 2002. As prescription rates increased so did non-medical use. Analysis of fatal cases in Iran showed a steady increase in tramadol-associated deaths (confirmed by toxicological analysis) in the period from 2005 to 2008. Among the 20,000 toxicological analyses carried out during this period, 294 cases (1.5%) showed tramadol exposure either alone (151 cases) or in combination (143 cases) with other drugs (in particular, opioids, antidepressants, and benzodiazepines).⁵⁰ A history of drug abuse was reported in 20% (60 cases) of these 294 cases.

During two months (April to May 2007), 114 cases of mixed tramadol intoxications (not confirmed by chemical analysis) were identified among 5850 admissions to the Teheran Poison Centre (Iran).⁹⁷ Co-ingestion of other substances (e.g., benzodiazepines) was common and (attempted) suicide (81% of cases) was the main reason for the ingestion. Seizures occurred in 35% of cases and two cases were fatal (tramadol dose 5 gram and 8.2 gram). These observations contributed to tramadol's classification as a controlled substance in Iran in 2007.

In China, abuse of tramadol led the Chinese State Food and Drug Administration to place tramadol under national control in 2007. As a result, tramadol use among drug abusers fell sharply from 13.3% in 2009 to 3.4% in 2011 but remained relatively high in the Guangdong province in South China.¹²¹ From their study among 23 tramadol abusers spontaneously referred to the addiction unit of the Medical Hospital in Guangzhou during a half-year study period (July up to December 2012), Zhang and Liu (2013) concluded that tramadol has a high risk of dependence in this study population and that dependence may be related to the use of high doses of tramadol for extended periods of time.¹²¹ This study does not give an indication of the magnitude of tramadol misuse.

The German study mentioned before confirmed the low abuse and dependence potential of tramadol after analysis of animal and human studies, and of two drug safety databases (WHO Vigibase and originator's safety database). From these two databases, the incidence of abuse or dependence was calculated as 0.12 and 0.21 cases per million defined daily doses (300 mg tramadol), respectively. The German expert group concluded that tramadol has a low potential for misuse, abuse, and dependence, and that abuse or dependence has a low prevalence in clinical practice in Germany.⁸¹

Analysis of Office for National Statistics (ONS) drug poisoning databases (study period 2000-2011) in England and Wales revealed that the number of tramadol mentions on death certificates increased from 87 in 2009 to 154 in 2011.^{2;44} In 35% of the cases between 2000 and 2011, tramadol was mentioned as the only drug (297 cases). This increase was paralleled by an increase in the number of tramadol prescription items dispensed, from 5.9 million Defined Daily Doses (DDDs) in September 2005 to 11.1 million in September 2012. In 2012, the number of tramadol mentions on death certificates in England and Wales has further increased to 175.⁷⁶ Apparently, there are no estimates of tramadol as the cause of death. Note that the mentioning of tramadol on a death certificate does not allow any conclusions on the cause of death. Largely because of this increase in tramadol-mentions on death certificates, the Advisory Council on Misuse of Drugs (ACMD) has recommended in 2013 that tramadol is controlled as a class C substance under the Misuse of Drugs Act 1971.²

The Uppsala Monitoring Centre (UMC) provided the WHO Secretariat with a summary file (received February 14th, 2014) of all adverse drug reactions (ADRs) that have been reported to the UMC in connection with tramadol, during the years 2006 to 2013. From this file, Tables 2 and 3 have been constructed. The data in Table 2 do not show a trend for drug abuse or drug dependence worldwide. The grand total of reports of tramadol abuse and dependence from 2006 up to 2013 was 661 and 327 cases, respectively. Of interest is the complete lack of data from some countries that recently have reported tramadol abuse and dependence in the (medical) literature (e.g., China, Egypt, and Iran). Table 2 separately shows the data for the USA, the United Kingdom (UK) and Germany, together with the number of reports concerning intentional overdose, suicide, suicidal attempt and death from tramadol in these countries. Of interest is the low number of reports from the United Kingdom as compared to Germany, including death reports, and the high number of suicides (525/557) and deaths (212/265) reported by the USA. Furthermore, the data show that the grand total of reports on drug abuse and dependence, worldwide, is primarily composed from the number of reports from the USA and Germany (91% for drug abuse and 58% for drug dependence).

Table 2. Number of database records on drug abuse and dependence worldwide, reported to the UMC from 2006 up to 2013.

	2006	2007	2008	2009	2010	2011	2012	2013	Grand total
Drug abuse	137	2	145	42	90	56	129	60	661
Drug dependence	33	3	84	34	35	78	25	35	327

Table 3. Number of UMC database records on drug abuse, drug dependence, intentional overdose, suicide, suicide attempt and death, as reported from the USA, the United Kingdom and Germany to the UMC in the period from 2006 up to 2013.

	USA	Germany	UK	Subtotals	Grand total, worldwide
Drug abuse	462	138	5	605	661
Drug dependence	131	59	28	218	327
Intentional overdose	153	102	15	270	301
Suicide	525	5	7	537	557
Suicidal attempt	128	112	2	242	262
Death	212	10	5	227	265

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

After scheduling tramadol in two USA states (Kentucky and Arkansas), the yearly trend of an increased number of poison centre calls concerning tramadol exposures was halted and a decrease in the number of cases was reported.¹⁰¹ From this study, no conclusions can be drawn about the number of adverse tramadol exposures relative to the number of legitimate prescription users. Additional data suggested that the number of people calling the Kentucky Regional Poison Center decreased proportionately with the number of people filling a prescription.²⁸ In other words, the decline in calls to the Kentucky Regional Poison Center was associated with less prescribing tramadol.

There is growing abuse of tramadol in some African and West Asian countries, as evidenced by recent large seizures of such preparations in North and West Africa. Abuse of tramadol has become a serious problem in Egypt and abuse has also been reported by Iran, Jordan, Lebanon, Libya, Mauritius, Saudi Arabia and Togo.⁴⁹ In 2010, an increase of non-medical use (abuse) of tramadol in Gaza was reported.⁸⁰

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

From the manufacturer's records on the total amount of tramadol used, the total amount of tramadol used worldwide in the period from 1990 to 2009 was calculated to be 11,758 million DDDs (1 DDD defined as 300 mg).⁸¹

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

16. Illicit manufacture and traffic and related information

There is evidence of increased trafficking in tramadol preparations to North and West Africa, as indicated by recent large seizures of such preparations in this region.⁴⁹

Egyptian authorities seized about 120 million tablets containing tramadol in 2011 and about 320 million tablets in the first quarter of 2012. According to information available to the International Narcotics Control Board (INCB), the preparations were smuggled into Egypt mainly from China and India. Saudi Arabia also reported increasing amounts of seizures of preparations containing tramadol. In Gaza, the number of drug arrests related to tramadol was 591 out of 1204 arrests in 2009, and close to two and half million tramadol pills were seized in 2009, compared to 550,000 in 2008.⁸⁰ In Benin, Ghana, Senegal and Togo (West Africa), large amounts of tramadol preparations, totalling more than 132 tons of such preparations, were seized between February and October 2012. The preparations had been concealed in sea containers sent from India and were intercepted by the local law enforcement authorities.⁴⁹

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

Tramadol is currently not under international control.

18. Current and past national controls

Legal status of tramadol differs internationally. In many countries, it is a prescription-only medicine.

Tramadol is not currently scheduled as a controlled substance by the U.S. Drug Enforcement Administration, but it is listed as a Schedule IV substance in Kentucky (since 2008) and Arkansas (since 2007) of the USA.

Tramadol is under national control in Bahrein since 2000, in Mauritius since 2000, in Australia since 2001, in Iran since 2007, in Sweden since 2008, in the Bolivarian Republic of Venezuela since 2008, in Ukraine since 2008, in Egypt (up-scheduled in 2009), and in Jordan and Saudi Arabia.

In China, the Food and Drug Administration has listed tramadol as a second category psychoactive substance in 2007.¹²¹

In February 2013, the Advisory Council on Misuse of Drugs (ACMD) recommended that tramadol is controlled as a Class C substance under the Misuse of Drugs Act 1971 in the United Kingdom.²

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of Tramadol

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 65 Member States answered the questionnaire for tramadol. Of these, 61 respondents (AFR 13, AMR 13, EMR 3, EUR 26, SEAR 2, WPR 4) had information on this substance.

LEGITIMATE USE

Sixty respondents stated that tramadol was currently authorized or in the process of being authorized/registered as a medical product in their country (AFR 12, AMR 13, EMR 3, EUR 26, SEAR 2, WPR 4). The earliest reported authorization is 1970 and its use is in the treatment of moderate to severe pain, both acute and chronic. The different formulations of tramadol reported are presented in the table below.

	Strength
Tablet	37.5mg; 50mg; 100mg; 400mg
Injection	50mg/ml; 100mg/ml
Capsule	50 mg ; 100 mg; 150mg; 200mg; 300mg
Drops	50mg/ml; 100mg/ml
Effervescent tablets	30mg; 50mg; 70mg
Suppository	100 mg
Prolonged release tablets	100mg; 150mg; 200mg; 250mg; 300mg
Solution for infusion	100mg/2ml
Combination tablets	37.5 mg tramadol/325 mg paracetamol

Brand names mentioned by the different respondents are included in the table below.

Name	Number of mentions
Tramal	28
Tramadol	15
Mabron	11
Nobligan	8
Zaldiar	7
Tradolan	6
Adamon	5
Zydol	5
Trabar	4
Trabilin	4
Tramacet	4
Tramadis	4
Tramadol Actavis	4
Tramadol Stada	4
Tramadol Vitabalans	4
Tramagetic	4
Zamadol	4
Domadol	3
Minidol	3
Tramadol Lannacher	3
Tramadon	3
Ultracet	3
Adorlan	2
Contramal	2
Dolex	2
Dolora	2
Domatra Plus	2
Pramol	2
Protradon	2
Tadol	2
Tr 100	2
Tradol	2
Tradonal	2
Tralgit	2
Trama	2
Tramada	2
Tramadol Alkaloid	2
Tramadol Aurobindo	2
Tramadol Hexal	2
Tramadol Krka	2
Tramadol Retard	2
Tramadol Retard Hexal	2
Tramadol Sandoz	2
Tramadol-M	2
Tramadol-Zdorovie	2
Tramagesic	2
Tramax	2
Tramazac	2
Tramium	2

Name	Number of mentions
Trasic	2
Ultram	2
Urgendol	2
<p>Aldoloffanalgecronicusdoloten, Algifeno, Amadol, Amanda Ammitram, Ana-Q (Ariston), Anadol, Analab, Analdol, Analgan Anamol Anangor, Astradol, Atradol, BioDol, Biotram, Boldol Bongesic Bongesic Plus, Calmador (Finadiet), Calmagesic Calmol, Calox, Capmadol, Cesalgin, Cesalgin,, Clo Q (Trb), Conzip, Crismal, Dalgion, Dalmatrol Dholo-Pax, Dolinof, Dolantag, Dolatramyl, Dolevar, Dolntag, Dolol, Dolol Retard UNO, Doloran, Doltram, Dolzam, Dorless, Dozem, Dubepan, Duodol, Duofem, Durotram, Eufindol, Galotram D, Gatadol, Gelotralib, Gemadol, Gemadol Retard, GenfarABL, Granions, Greatamol, Himmadol, Huons Tramadol HCL, Iptramol, Ixprim, Ixprimzaldiartopalgic, Ketal Duo, Matrix, Ketalar, Larapram SR, Lisan, Lodam, Maditer, Madol, Madola, Mandolgin, Mandolgin Retard, Manol, Marol, Matradol, Matrix, Maxitram SR, Medley, Medroff, Megador, Metagesic, Modsenal, Naxodol, Naxodol Plus, Noax, Noax Uno, Normal, Nytradol, Opidol, Oratram, Pacmadol Padol, Paindol, Painol, Paratram, Paratramol, Paxilfar, Pengesic Pharmadol, Pluzadol, Poltram, Poltram Retard, Pontalsic, Profundol Pyredol, Ralgen, Ramadol, Rapitram, Raven, Recalm, Relon, Revange, Rofy, Rolenal, Sanadol, Sefmal, Sensitram, Sinedol Sonamol, Souladol, Strom, Supragesic-T (Beta), Sylador, T Dol 100 Tamadol, Tambol, Tamolan, Tasidol, Technodol, Theradol, Tialgintram, Timarol, Timasen SR, Tindol, Tiparol, Tolmus. Toral, Tracap, Tracidol, Tracine, Tradiol, Tradogesic, Tradorec XL, Tradoxil, Tradoxil, Tragesic, Tral, Tral P, Tralex, Trama Klosidol (Bago), Tramabene, Tramacap, Tramache, Tramacontin, Tramacort, Tramaden, Tramadex, Tramadil, Tramadin, Tramadol Jaka, Tramadol Lek, Tramadol AL, Tramadol EG, Tramadol Farmal Retard Tramadol Genfar, Tramadol HCl 50 PCH, Tramadol HCl Apotex Tramadol HCl Ratiopharm, Tramadol HCl Sandoz, Tramadol Hydrochloride, Tramadol LS, Tramadol Mylan, Tramadol Retard Actavis, Tramadol Retard Medartuum, Tramadol Retard Sandoz, Tramadol Synteza, Tramadol Teva, Tramadol-ZN, Tramadol-M Tramadol, Tramadol ID 150mg, Tramadolten, Tramadoltramal Tramagen, Tramakard, Tramakat, Tramake, Tramakress, , Tramalgin Tramaliv, Tramamed, Tramanovag, Tramapine, Tramasol, Tramateg Tramateg Plus Tg, Tramavolta, Tramcet Combination Tablets, Tramed, Tramedif, Tramedo, Tramgesic- Zodid, Tramoda, Tramodyne, Tramól-L, Tramolan, Tramomet, Tramox, Tramquel SR Tramudin, Tramulinum, Tramundin, Tran-u-ron, Tranofen, Trapidol Traumed, Tremadol, Tridural, Trimma, Trodon, Troma, Trosic, Updol Vesnon-V, Volcidol, Xymel, Yodalamart, Zafin, Zaledor, Zalviar, Zamudol, Zeridame SR, Zetawin Plus, Zodol, Zygard, Zytram</p>	1 each

The following products containing tramadol and paracetamol were also mentioned:

Acutral, Acutral Effervescent, Anaki, ApoPatram, Curidol, Delpran, Doreta, Exbol Hipatra, Padolten, Paratram, Parcotram, Poltram Combo, , Sedoloris, Strenduo Symtram, Tracemol, Genoptim, Tramapar, Teva, Tramcet, Traparac, Zaldiar, Zaldiar Algopara, Zaldir Tramadol/Paracetamol EG

Thirteen respondents mentioned that tramadol was used in medical or scientific research. No other legitimate uses were reported. Forty respondents stated that their countries imported Tramadol, 3 manufactured it in their own country and 5 manufactured and imported Tramadol. The estimated use reported ranged from less than 1 g to over 20,000 kg. Several respondents did not have this data available.

HARMFUL USE

25 respondents confirmed that there was recreational/harmful use of tramadol and 12 stated that there is no such use. The common routes of administration were reported as oral by 14, oral/injection by 5 and one each inhaling/sniffing, injection and oral/inhaling/sniffing. This was obtained through diversion by 10, diversion plus trafficking by 6, trafficking alone by three and clandestine manufacturing by one. Common formulations of tramadol reported were tablet by 12, tablet and liquid forms by seven, and powder/tablet and powder/ tablet/ liquid one each. The reported use was by general population in seven response and in clubs in two responses. Five respondents report deaths related to tramadol use; 3, 4, 6, 20 (2012) and 154 (2011) respectively. One respondent stated that tramadol along with other substances were found in some fatalities. Addiction programme enrolment is reported by two respondents, 26 and approximately 30-80 respectively. One respondent reported 191 emergency room visits in 2012. Data for 2011 is provided by 1 respondent with 6 deaths and 54,000 emergency room visits. One respondent reported that , ‘there were a total of 12,424 tramadol exposures in 2011. Of these, there were 6,361 single substance exposures (6 deaths) associated with tramadol. In 2011 the estimates of all emergency department visits associated with tramadol products was more than 54,000 nationally, or 17.5 visits per 100,000 population. The estimated number of misuse related emergency department visits, which are classified as AllMA ED visits, was almost 22,000, or 7 visits per 100,000 population.’

One report suggests a rise in tramadol use during recent years.

Fourteen respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by tramadol. This includes a report of 13 cases of tolerance and six cases of withdrawal. Tramadol is reported to produce a number of symptoms relating to central nervous system and gastrointestinal tract, similar to other opioids. High doses of tramadol, often in combination monoamine oxidase (MAO) inhibitors or serotonin-selective reuptake inhibitors (SSRIs), have been associated with a serotonin syndrome consisting of convulsions, hyperthermia, muscle rigidity and pain.

CONTROL

Of those with information available on this substance, 47 reported that Tramadol was controlled under legislation that was intended to regulate its availability; 19 under “controlled substance act”, 20 under “medicines law”, 1 under “analogue legislation”, 1 under “generic legislation” , 1 under ‘poison act’ and 5 under “other” laws. Eleven respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving tramadol, one reported synthesis of the product and another processing into consumer product; 4 reported trafficking, 11 reported diversion and 7 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures*	1,795 (7)	2,121 (8)
Total quantity seized (kg)	2.03 (2)	10.02 (3)
Total quantity seized (L)	0.05 (1)	0.02 (1)
Total quantity seized (ampoule)	1 (1)	43 (1)
Total quantity seized (tablets/pills)	1,495 (3)	18,734 (4)

*An additional 7 respondents reported zero seizures in 2011 and 2012

IMPACT OF SCHEDULING

Forty-eight respondents reported that if tramadol was placed under international control, they would have the laboratory capacity to identify the substance. Eight respondents indicated that the availability for medical use would be affected if placed under international control.