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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 as a mu agonist on the 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, physical dependence of the opioid type can occur with tramadol when used for a sustained period of time. Physical dependence on tramadol may occur when used within the recommended dose range of tramadol. In many individuals with tramadol misuse, a substance abuse history is found. Orally administered tramadol can produce opioid-like effects (both mentally and physically). Tramadol is generally considered a medicine with a lower abuse potential compared to morphine, but abuse of tramadol can occur and does occur. 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. 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. Websites provide many user reports on the non-medicinal use of tramadol.
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 Chemical Names
   (±)-cis-(2-dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol

D. Trade Names

E. Street Names
Chill pills, Oxyontin Lite, Trammies, Ultras

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

G. WHO Review History
Tramadol has been considered by the WHO five times: in 1992, 2000, 2002, 2006, and 2014. This compound was first pre-reviewed at the 28th meeting of the Committee (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 a significant numbers of cases of a 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. Tramadol was again 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. The Committee reviewed tramadol most recently (the fifth time) at its 36th meeting in 2014, and based on the evidence available regarding dependence, abuse and risks to public health recommended that a critical review of tramadol was not warranted at that time. A pre-review of tramadol was recommended based on information received by the WHO Secretariat regarding the misuse of tramadol.

2. Chemistry

A. Chemical Name

IUPAC Name:
(1S,2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol

CA Index Name:
tramadol

B. Chemical Structure

(-)-Tramadol

(Image available from PubChem[1])

Free base:
Molecular Formula: C₁₆H₂₅NO₂
Molecular Weight: 263.4 (base); 299.8 (hydrochloride salt)
C. **Stereoisomers**

Tramadol has two chiral centers 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-configuration [2], and the methoxyphenyl group and the dimethylaminomethyl group in trans-configuration.

D. **Methods and Ease of Illicit Manufacturing**

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. [3, 4] The chemical synthesis of tramadol and two of its metabolites has been described by the same coupling reaction using organolithium derivatives. [5]

The National Centre for Biotechnology (NCBI) PubChem states that a Grignard reaction of 2-(dimethylaminomethyl)cyclohexanone (obtained by Mannich reaction of cyclohexanone, formaldehyde, and dimethylamine hydrochloride) and the Grignard reagent of 3-bromoanisole yields tramadol as a cis/trans mixture (cis:trans = 85:15). Tramadol (cis isomer) is separated from the reaction mixture by crystallization of the hydrochloride salt. ... The trans isomer can be epimerized to the cis isomer by strong acids. [1]

E. **Chemical Properties**

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. [6, 7]

- **Melting point:** 180-181 °C
- **Boiling point:** no data
- **Solubility:** water soluble; methanol soluble

F. **Identification and Analysis**

Tramadol may be identified chemically by infrared spectroscopy, mass spectrometry, and nuclear magnetic resonance. [8] Many analytical methods for the identification and quantification of tramadol and major metabolites in body fluids have been described in the literature (see Baselt 2011 and Smyj et al 2013 [8, 9]). Gas and liquid chromatographic techniques are available.
The enantiomeric separation of tramadol and metabolites by chiral chromatography has also been described. [10, 11]

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**

   A. **Routes of administration and dosage**

   Tramadol is marketed as the hydrochloride salt and is generally used in the oral form (as tablets or capsules). Online sources indicate that it can be a parenteral form (most typically, intravenous, although such as form could be used subcutaneously or intramuscularly) in some countries (e.g., India), and a rectal form (e.g., Bangladesh). Other online resources suggest that it is available in a variety of other pharmaceutical formulations, such as sublingual drops, and an intranasal form, although it is not clear if these are currently available marketed forms.

   Tramadol is also available in combination with acetaminophen (paracetamol). Immediate-release and extended-release oral formulations are available. The following pharmaceutical formulations are available for oral use:

   - 50 mg immediate-release (IR) tablets/capsules
   - 50 mg; 100 mg; 150 mg; 200 mg; 300 mg; and 400 mg extended-release (ER) tablets/capsules
   - 37.5 mg tramadol combined with 325 mg acetaminophen tablets/capsules
   - various doses of a combined IR + ER forms of tramadol capsules (i.e., variable release): 25 mg + 75 mg; 50 mg + 150 mg; 50 mg + 250 mg (IR + ER, respectively)

   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 24 hours. Extended-release preparations are better tolerated and are dosed once daily.

   B. **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. [12]
**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. [12, 13]

Peak plasma concentrations of tramadol after single dose oral administration (100 mg) are 0.31 +/- 0.08 mg/L. [12] 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). [12] Twenty-three metabolites have been identified. [14] 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). [15, 16]

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 metabolizers have relatively low plasma concentrations of O-desmethyltramadol, whereas (ultra)rapid metabolizers 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 feces (10%). About 30% of an oral dose is excreted unchanged in the urine, and about 60% in the form of free and conjugated metabolites. [6, 9]

The elimination half-life of racemic tramadol is approximately 6 hours, irrespective of the mode of administration, and about 8 hours for O-desmethyltramadol. [9] Half-lives may be prolonged in people with decreased liver or kidney function. [12]

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. [12]
C. 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 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. [6, 7, 17] 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).

(+/-)-Tramadol binds with low affinity to the human μ-opioid receptor with an affinity constant (Ki) of 2.4 μM. 42 This affinity is approximately 4000-fold less than that of morphine (Ki = 0.34 nM). The affinity of tramadol for the δ- and κ-opioid receptors is even less (Table 1). The (+/-)-O-desmethyl metabolite (M1) of tramadol, on the other hand, shows about 400-fold higher affinity for the μ-opioid receptor (Ki = 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 (Ki = 3.4 nM) and not the (S) (-)-enantiomer (Ki = 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 (+/-)-tramadol. The metabolite (+/-)-M5 also has a higher affinity than (+/-)-tramadol for the μ-opioid receptor (Ki = 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. [6, 18]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ki (μmol/L)</th>
<th>opioid receptor affinity</th>
<th>uptake inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>μ (human)</td>
<td>μ (rat)</td>
</tr>
<tr>
<td>(+/-)-Tramadol</td>
<td>2.4</td>
<td>2.1</td>
<td>58</td>
</tr>
<tr>
<td>(+)-Tramadol</td>
<td>1.3</td>
<td>62</td>
<td>54</td>
</tr>
<tr>
<td>(-)-Tramadol</td>
<td>24.8</td>
<td>213</td>
<td>54</td>
</tr>
<tr>
<td>(+/-)-M1</td>
<td>0.0054</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)-M1</td>
<td>0.0034</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-)-M1</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>0.00062</td>
<td>0.00034</td>
<td>0.092</td>
</tr>
</tbody>
</table>

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%) antagonized tramadol-induced analgesia and that quinidine (an inhibitor of hepatic demethylation of tramadol into M1) inhibited tramadol-induced miosis but hardly affected tramadol analgesia. [21] In addition, Desmeules et al (1996) found that yohimbine (an alpha-2-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). [22] 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. [6] (+)-Tramadol is the enantiomer with highest activity as a serotonin releaser and reuptake inhibitor in rat dorsal raphe nucleus brain slices. [23] The (+)-enantiomer is about four times more potent than the (-)-enantiomer as serotonin reuptake inhibitor. [24] Besides, tramadol is an effective blocker of noradrenaline reuptake in rat spinal cord synaptosomes by blocking the noradrenaline transporter. [25] As a noradrenaline reuptake inhibitor, (-) tramadol is about ten times more potent than (+)-tramadol in rat hypothalamic synaptosomes. [24]

Minami et al. (2007) reviewed the effects of tramadol on monoamine transporters and G-protein coupled receptors. [26] 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. [26]

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 as a releaser and reuptake inhibitor of serotonin, and as a reuptake inhibitor of noradrenaline, and its metabolite (M1) 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.

5. Toxicology

Carcinogenicity
Animal studies do not reveal a carcinogenic effect of tramadol. Reproductive and developmental toxicity studies have been negative. In addition, mutagenicity studies do not show evidence of a genotoxic risk to man. [27]
Fatalities
Compared to the classical opioid analgesic morphine, tramadol is considered to be a relatively safe analgesic (cases of fatal poisoning due to tramadol alone have been reported in the literature over the years; [28-36]). More frequent are intoxications with co-ingestion of other drugs or alcohol [29, 35-41] 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. [12, 42, 43] Moreover, in combination with serotonergic agents (in particular, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors) tramadol may induce the serotonin syndrome [44-50] The hyperthermia in the serotonin syndrome is potentially fatal.

Respiratory depression
Opiates reduce the sensitivity of the respiratory center 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 been observed in overdose cases of tramadol. [51-53] However, at therapeutic doses tramadol is not likely to cause significant respiratory depression. [6]

In healthy subjects, tramadol reduced the sensitivity to carbon dioxide, but did not reduce the ventilatory response to hypoxia. [54] At therapeutic doses, tramadol produced less respiratory depression, both in adults and in children, compared to morphine, pethidine, and oxycodone. [55-59] In neonates undergoing surgery in Benin City (Nigeria), tramadol provided adequate analgesia without significant complications. [60] Nevertheless, in patients at risk for respiratory depression, the use of tramadol is contra-indicated. [12, 61]

Cases of tramadol-related respiratory depression have been described in the literature. [51-53] Intravenous naloxone has been successfully used to reverse the opioid effects of tramadol overdose [52, 62]

For example, a male patient with acute respiratory distress syndrome had a blood concentration of 9.5 mg/L tramadol, without toxic levels of other drugs [53] 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. [51] 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. [63] 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). Note, however, that this study lacked laboratory confirmation of tramadol-only poisoning. [64]

**Cardiac Effects**
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. [28, 39, 43, 65] Case reports of cardiogenic shock [66, 67] associated with tramadol overdose have appeared in the literature, but are relatively rare and may represent unusual clinical scenarios. These case histories show that fatal or near-fatal intoxications are associated with supra-therapeutic doses (overdoses) of tramadol and that intoxication at therapeutic doses is rare.

**Seizures**
Rarely, seizures occur at therapeutic doses of tramadol. Tramadol-related seizures appear to be mainly associated with doses exceeding the maximum recommended dose of 400 mg per day. [44, 62, 68-74] Seizure risks of up to 54% of cases (overdose or abuse) have been found in some studies, with the risk related to the dose of tramadol ingested. Recurrent seizures are not common and the usual outcome is full recovery. [75] ECG parameters are not predictive for seizures. [76] Symptoms of seizures after tramadol ingestion have also been reported in infants. [77, 78]

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. [62] 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. [79]

Another retrospective study conducted in the USA used Poison Control Center data to compare tapentadol and tramadol toxicity (217 and 8566 cases of sole ingestion, respectively). [80] The most common clinical effects associated with tramadol were drowsiness/lethargy (25.4%), tachycardia (16.5%), and seizures (14.6%).

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. [81] (+)-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%), diarrhea, 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%). [12, 82, 83]

Physical dependence on tramadol may occur, and is addressed more fully in the next section. [84-86] Withdrawal reactions can include restlessness, agitation, anxiety, sweating, insomnia, hyperkinesia, tremor, paresthesias, and gastrointestinal symptoms, consistent with opioid withdrawal symptoms. [86-89]

The incidence of adverse effects depends on the dose and the mode of administration. [6, 16] Sustained-release preparations show a better tolerability profile. [13] One report from the USA has shown an increase in emergency department (ED) adverse event visits associated with tramadol, more than doubling between 2005 and 2009, with relative stability in the following years. [90] However, these absolute numbers were not corrected for the number of prescriptions of tramadol, and rates of visits would be more informative.

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 $10^5$ patient-years, which was significantly higher than for the dextropropoxyphene-paracetamol combination (24.9) and the codeine-paracetamol combination (12.5). [91] 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.

7. **Dependence Potential**

   **A. Animal Studies**

   Animal studies showed that physical dependence on tramadol may develop, but this is not consistently seen in all studies. [92] In rhesus monkeys, only mild to moderate withdrawal symptoms were detected (see review [93]).

   **B. Human Studies**

   Tramadol can produce opioid physical dependence. Opioid-like withdrawal symptoms have been demonstrated with chronic dosing (consistent with the need for accumulation of the M1 metabolite in order to see opioid effects). Studies show that tramadol physical dependence may occur when used daily for more than a few weeks.

   **Human laboratory studies**

   In an early human laboratory study that enrolled non-dependent opioid users, intramuscular tramadol was placebo-like at doses of 75 and 150 mg, while a 300
mg dose was identified as morphine-like but was otherwise not associated with typical abuse liability measures. [94]

In dependent opioid abusers, intramuscular tramadol was shown to act as a mild opioid agonist, able to suppress opioid withdrawal symptoms, though statistically not to a significant degree, comparable to hydromorphone. [95] In this study, tramadol did not show opioid antagonist effects. In another human laboratory 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). [96]

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. [97] 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.

Precipitated withdrawal intensity was studied in a group of opioid-dependent adults who were initially maintained on 60 mg (15 mg q.i.d.) subcutaneous morphine maintenance, and then two different daily oral doses of tramadol (200 mg/day and 800 mg/day, respectively), with each tramadol dosing period lasting 4-weeks. [86] Acute tramadol 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 the 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, but that it did not produce significant cross-tolerance.

Clinical reports
In many cases of tramadol physical dependence, a history of substance abuse is present. [98, 99] However, dependence does also occur in individuals without a substance abuse history. [84, 100]

Zhang et al (2013) studied tramadol dependence in users without a history of substance abuse. [101] According to the authors, tramadol became a drug of abuse after its introduction in China as a non-controlled analgesic medicine. After being placed under national control in 2007, tramadol use among drug abusers declined from 13.3% in 2009 to 3.4% in 2011. However, use remained relatively high in some regions. Therefore, the authors started a study to characterize tramadol-dependent users spontaneously visiting an 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.

In a 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. [102] 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.

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). [99] 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. Hospitalization was reported in 50% of the cases, mostly in a psychiatric or
dependence clinic.

Occasionally, withdrawal symptoms of tramadol dependence have been treated
effectively with buprenorphine-naloxone. [103]

Summary on dependence potential
In summary, the data on the dependence potential of tramadol show that tramadol
can produce physical dependence, but that physical dependence is associated with
the use of tramadol under chronic dosing conditions (i.e., over an extended period
of time – a matter of weeks). 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

A. Animal Studies

Based on animal studies, tramadol is an atypical opioid analgesic with mild opioid-
like effects (see review [93]). Based on self-administration in monkeys, tramadol
has some abuse potential but less so than morphine. In one rat model of self-
administration under a fixed-ratio and progressive-ratio schedule, tramadol acted as
a weak reinforcer of self-administration compared to remifentanil and morphine.
[104] A second rat study that examined the pharmacological characteristics of
tramadol using self-administration and conditioned place preference procedures
found effects consistent with the potential for physical dependence and abuse potential. [92]

B. **Human Studies**

Human laboratory studies

Human studies show that tramadol has a low abuse potential relative to the prototypic opioid morphine (see review [93]). Opioid-like effects can be produced by oral administration of tramadol, but these are mild and not produced by parenteral administration. [93] 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. [94]

A human drug discrimination study demonstrated the opioid activity of oral tramadol. [105] 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 identified 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 scores on a 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.

In contrast, oral tramadol appears to act as a reinforcer in non-dependent opioid abusers, comparable to oxycodone. [106] 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 a 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.

In a study that enrolled recreational drug users (n=22), 100 mg oral tramadol was found to induce effects of ‘drug liking’ and ‘want to take again’. [107] The drug ratings were comparable to those of 25 mg morphine but lagged behind those of morphine in some subjects. These findings indicate that tramadol has abuse liability in recreational drug users.
Finally, a within subject study of 10 withdrawn drug users compared the acute intramuscular effects of tramadol (100 mg), buprenorphine (0.6 mg), and placebo [108]. In this study, tramadol produced acute subjective effects, and in general had greater opioid-like effects than placebo, but less so than buprenorphine.

Clinical reports and post-marketing surveillance
A history of drug abuse is frequently detected among tramadol abusers. [99, 109, 110] Data indicate that there is a growing number of tramadol abusers, in particular in some Middle East countries. [73, 111-113] For example, in a study from Iran, the association of tramadol use and use of other psychoactive substances was investigated in high school students (n=1894; response rate 95%). [112] 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). [73] A history of chronic tramadol abuse was found in 34 cases.

In the United States, tramadol was introduced onto the market in 1994 as an analgesic. Several post-marketing studies have been published since. Data from the first post-marketing surveillance program, which started shortly after the introduction of tramadol in that country, 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). [114] 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. [115] 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. [116]

Further monitoring in the USA up to 2004 showed that the rates of abuse remained stable, despite the introduction of new brands and new generic formulations. [110] Again, this line of research/monitoring found that abuse was almost exclusively (95%) in individuals with a history of substance abuse.

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) conducted in the USA. [117] 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. The abuse rates for tramadol and NSAIDs were significantly less than the abuse rate for hydrocodone.

A report from the USA on emergency department (ED) visits for tramadol misuse or abuse more than doubled between 2005 and 2010, with the majority of patients having concurrent abuse of another substance. [118]

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. [102]

9. **Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use**

**Analgesia**

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 [6, 13, 16, 17, 102, 119]), and is available worldwide 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. [120] In chronic non-cancer pain, tramadol may be appropriate when non-opioid analgesics are ineffective or contra-indicated.

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 pain [121], some effect (low quality evidence) in chronic low back pain [122], and a modest effect (fair evidence) in chronic osteoarthritis [123-125]. Manchikanti et al. (2011) [124] concluded that the evidence for tramadol in managing osteoarthritis pain (knee and multiple joints) was fair, and that the evidence was poor in all other conditions of chronic non-cancer pain.

A recent Cochrane review meta analysis by Wiffen [126], that looked at the use of tramadol for chronic pain related to the presence of a malignant tumor, found limited and low quality evidence that this medication produced pain relief. Similarly, another Cochrane review meta-analysis carried out in 2017 found limited and low quality evidence supporting the efficacy of tramadol in the treatment of neuropathic pain. [127] Another recent systematic review and meta analysis of tramadol for neuropathic pain concluded
with a weak recommendation for tramadol’s use as a second line agent. [128] However, these reviews may speak less to the efficacy of tramadol for these conditions, and more to the lack of high quality trials that can provide a database supporting the use of tramadol for the treatment of chronic cancer or neuropathic pain.

In a review by a German expert committee (described above), 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. [102] 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 guidelines [129]).

The treatment of opioid withdrawal
Reports on the use of tramadol for the treatment of opioid withdrawal have periodically appeared in the literature. (See, for example, [130-133]) Tramadol is not indicated for this condition. A recent randomized, controlled trial compared tramadol ER to clonidine and buprenorphine for medically managed opioid withdrawal in 103 opioid dependent patients. [134] In this study, tramadol was generally more effective than clonidine and comparable to buprenorphine on treatment retention and withdrawal suppression, and interestingly did not show the rebound withdrawal seen after buprenorphine treatment ended.

10. Listing on the WHO Model List of Essential Medicines
Tramadol is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List). [135]


11. Marketing Authorizations (as a Medicinal Product)
12. **Industrial Use**

Industrial use of tramadol is not reported.

13. **Non-Medical Use, Abuse and Dependence**

Tramadol is advertising as being available via the Internet without a prescription, although it is not known if these sites are actually providing tramadol. The website EROWID, and other websites as well, provide user reports of the non-medicinal use of tramadol.

**United States**

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). [114] 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. [115] Reporting bias and non-representative sampling of cases may have underestimated the true incidence of abuse. [116] Further monitoring up to 2004 showed that the rates of abuse remained stable, despite the introduction of new brands and new generic formulations. [110] This study confirmed that abuse was found almost exclusively (95%) in individuals with a history of substance abuse.

**Iran**

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). [111] 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). [43] 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.

A survey study with 1894 grade 10 students found that the lifetime prevalence of tramadol misuse was 4.7% [112] in the city of Ilam, Iran. In this study, a lifetime history of tramadol misuse was associated with cannabis, alcohol, and ecstasy use in the month prior to the survey.
China
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. [101] From a 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. This study does not give an indication of the magnitude of tramadol misuse.

France
An analysis of different surveillance methods used to assess tramadol abuse in France concluded that there was not a major public health issue with the use of this medication in that country [137]. Notably, these different methods do find cases of misuse and abuse, as well as physical dependence on tramadol.

Egypt
Tramadol misuse in Egypt has been a growing concern. [138] A report from The National Council for Drug Control and Treatment (Egypt) noted that the proportion of people seeking treatment for tramadol addiction has been steadily increasing between 2011 (38.7% of “total addicts” were “tramadol addicts”) and 2016 (71.1%). [139] It appears that much of the tramadol being abused in Egypt is imported from India.

A study of 204 school students in Egypt found that 8.8% of them had a urine drug screen positive for tramadol [140], and among those who admitted tramadol use, the most common frequency of self-reported use was once per month. A study with focus groups of Egyptian youth found tramadol was the most commonly used pharmaceutical drug. [141]

The absolute number of persons seeking treatment for tramadol addiction, as assessed by hot line data, increased between 2011 and 2012 (3320 and 8313), as did the proportion of all calls related to tramadol (38% and 39%) [142].

Germany
The German study mentioned before noted 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. [102]

United Kingdom
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. [29, 143] 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 was 175; this increased to a peak of 240 in 2014, but then trended back down in 2015 and 2016 (with 208 and 184 deaths, respectively). Note that the mentioning of tramadol on a death certificate does not allow any conclusions on the cause of death. Largely because of the increase in tramadol-mentions on death certificates, the Advisory Council on Misuse of Drugs (ACMD) recommended in 2013 that tramadol be controlled as a class C substance under the Misuse of Drugs Act 1971.

A UK internet survey (n=7,360) of nonmedical use of tramadol found that 5% (326 respondents) had used tramadol in the past year. While most tramadol was obtained by prescription, there were 163 respondents who used tramadol for reasons other than pain relief. These findings suggest there is a relatively small number of persons in the UK who misuse tramadol. A large analysis of opioid prescription exposures between 2008 and 2012 found that the incidence of tramadol use disorder was stable.

Columbia
An observational (retrospective) study of opioid misuse in hospitalized patients in Medellin, Columbia found a relatively small number of persons with DSM-IV opioid dependence (n=60). However, the most common diagnosis, in 37 of the 60, was tramadol.

Worldwide, other countries
The Uppsala Monitoring Centre (UMC) provided the WHO Secretariat with a summary file (received August 23, 2017) of all adverse drug reactions (ADRs) that have been reported to the UMC in connection with drug abuse or dependence of tramadol, during the years 1984 to 2017. While sporadic reports appear in the early years, it was not until 1996 that some more consistency in these reports started to occur. The numbers by year are presented in Table 2.

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug Abuse</th>
<th>Drug Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>1997</td>
<td>0</td>
<td>106</td>
</tr>
<tr>
<td>1998</td>
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<td>15</td>
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<td>1999</td>
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<tr>
<td>2000</td>
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<td>101</td>
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<td>2008</td>
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<td>83</td>
</tr>
<tr>
<td>2009</td>
<td>23</td>
<td>34</td>
</tr>
</tbody>
</table>

After scheduling tramadol in two USA states (Kentucky and Arkansas), the yearly trend of an increased number of poison center calls concerning tramadol exposures was halted and a decrease in the number of cases was reported. [148] 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. [149] 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 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. [150] In 2010, an increase of non-medical use (abuse) of tramadol in Gaza was reported. [113]

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). [102]

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. [150] 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. [113] In Benin, Ghana, Senegal

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Calls</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>66</td>
<td>38</td>
</tr>
<tr>
<td>2011</td>
<td>32</td>
<td>54</td>
</tr>
<tr>
<td>2012</td>
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<td>23</td>
<td>32</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1526</td>
<td>982</td>
</tr>
</tbody>
</table>
and Togo (West Africa), large amounts of tramadol preparations, totaling 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. [150]

Data provided by the UNODC on global tramadol seizures was provided for this report (July of 2017). These data showed a steady rise in seizures between 2007 (when 0.00545 kg were seized) and 2015 (when 111,846 kg were seized). Virtually all of the seizures in 2015 were associated with Benin (111,800 kg), but the pattern in seizures by country varied on a year-by-year basis. Thus, for example, in 2014 total seizures were 25,079 kg, which were predominantly Jordan (14,416 kg). In 2013, total seizures were 1271 kg, which were predominantly Saudi Arabia (722 kg).

17. **Current International Controls and Their Impact**

Tramadol is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. **Current and Past National Controls**

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

When tramadol was initially approved for use in the United States, it was not scheduled as a controlled substance by the U.S. Drug Enforcement Administration. However, in 2014 the U.S. reclassified it as a Schedule 4 controlled substance.

Tramadol is under national control in Bahrain 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. [101]

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. [143]

19. **Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance**

None.
References


139. El-Gaafarawi, I., Tramadol Problem in Egypt; Briefing.

Please refer to separate Annex 1 document published on ECDD website