Critical Review Report:

Tramadol

Expert Committee on Drug Dependence

Forty-first Meeting

Geneva, 12-16 November 2018

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Contents

Acknowledgements

This report was prepared by the Secretariat of the Expert Committee on Drug Dependence (ECDD) within the Department of Essential Medicines and Health Products (EMP) of the World Health Organization (WHO), Geneva, Switzerland. The WHO staff involved in the production of this document, developed under the overall guidance of Mariângela Simão (Assistant Director General, Access to Medicines, Vaccines, and Pharmaceuticals), Suzanne Hill (Director, Essential Medicines and Health Products), Gilles Forte, (Secretary of the Expert Committee on Drug Dependence) were Dilkushi Poovendran (Technical Officer, WHO Essential Medicines and Health Products) and Wil De Zwart (Technical Officer, WHO Essential Medicines and Health Products). WHO would like to acknowledge Kim Wolff for the literature review and drafting and Jurgen Rehm, Astrid Otto, and Jakob Manthey for questionnaire analysis and report drafting.

Executive Summary

Substance identification
Tramadol hydrochloride is a white, bitter, crystalline and odourless powder soluble in water and ethanol. It is an atypical, weak, phenylpiperidine opioid analgesic.

WHO Review History
Tramadol was pre-reviewed at the 39th ECDD meeting (November 2017) and it was recommended that tramadol be subject to a critical review.

Chemistry
The chemical name of tramadol hydrochloride is (±) c/s-2-((dimethylamino) methyl)- l-(3-methoxyphenyl)-cyclohexanol hydrochloride.

Ease of convertibility into controlled substances
Tramadol is not likely to be converted into a controlled substance

Similarity to known substances / Effects on the central nervous system
Tramadol is a weak opioid and well known as an analgesic that produces opioid-like effects primarily due to its metabolite, O-desmethyltramadol (M1). The analgesic effect of tramadol also involves noradrenaline and serotonin receptor systems. Tramadol was the first medication in its class to produce dual-analgesic effects, acting synergistically as an opioid agonist and monoaminergically as a serotonin and noradrenaline reuptake inhibitor

General pharmacology
Tramadol is a prodrug that is metabolised by cytochrome P450 (CYP) enzymes CYP2D6 and CYP3A4 to its more potent metabolites particularly O-desmethyltramadol (M1) as well as N, O-desmethyltramadol (M5). Tramadol and its metabolites are stereoselective and display high interindividual variability in clinical efficacy correlating with the activity of the genetically polymorphic enzyme CYP2D6. Current and emerging data suggest that the analgesic efficacy of tramadol differs according to different CYP2D6 genotypes: Poor Metabolisers (PM) experiencing better pain relief than intermediate metabolisers (IMs) who may experience insufficient relief. Ultra-rapid metabolisers (UMs) being more likely to experience adverse effects from tramadol because of the more rapid release of M1. Of additional relevance is the significant interethnic differences in CYP2D6 allele frequencies demonstrated across many countries. The highly variable efficacy of tramadol for pain relief is further complicated by its dual pharmacological properties as both an opioidergic and a monoaminergic drug. Modulation of enzyme CYP2D6 activity by drug interactions and/or genetic polymorphisms may alter the pharmacodynamics of the drug so that opioidergic properties are more pronounced in CYP2D6 UM, whilst CYP2D6 PMs, may move towards a monoaminergic antidepressant-like molecule devoid of opioidergic activity. The likelihood of such events having significance either in clinical practice or in the aetiology of tramadol abuse and/or dependence has not been clearly articulated.

Toxicology
In a marketing authorisation application (Pfizer, 50 mg capsules) tramadol was classified as non-mutagenic following studies on the tumorigenic potential of tramadol hydrochloride in

rats and mice. Few studies exist regarding the risk of a teratogenic effect in humans. Use of tramadol in early pregnancy identified using the Swedish Medical Birth Register, found 1751 women (1776 infants) had used tramadol, 96 of the infants had a congenital malformation (70 were relatively severe). The adjusted odds ratio (OR) for a relatively severe malformation was 1.33 (95% CI 1.05-1.70). The OR for cardiovascular defects in infants was 1.56 (95% CI 1.04-2.29) and for pes equinovarus 3.63 (95% CI 1.61-6.89) and were significantly increased. The study suggested a moderate risk of teratogenic effect of tramadol.

Adverse reactions in humans

Common side effects include dizziness, nausea, constipation, and headache. In overdose multiple systematic symptoms reflecting the multimodal activity of tramadol (involving μ-opioid receptor, nor adrenergic and serotonergic systems and monoamine oxidase inhibitor (MAOI) activity) are apparent. Symptoms including lethargy, nausea, tachycardia, agitation, hypertension, respiratory depression, seizures and coma have been reported. It is well established that both tramadol and its primary metabolite M1 inhibit the reuptake of serotonin and noradrenaline and therefore its use may risk non-opioid adverse events, including serotonin syndrome. Tramadol-induced seizures, respiratory depression, cardiovascular and renal complications are adverse effects of supratherapeutic dosage consumption. The multimodal activity of tramadol should be borne in mind when assessing the risk of this compound to the public.

Dependence potential

Many cases of dependence have been described among individuals with a history of substance abuse. Physical dependence and withdrawal symptoms have also been described in long-term, infrequent users, who consume high doses of tramadol without a history of misuse of other substances and this behaviour is thought to pose a clear risk of dependence. There is growing evidence that the development of physical dependence to tramadol is dose-related, and administration of supratherapeutic doses lead to a similar dependence profile to morphine. Whereas the risk of physical dependence is lower than prototypic opioids when low-dose tramadol is used over an extended period. Dependent individuals, who appear to be predominantly male, and under 30 years of age, who consume supratherapeutic amounts of the drug, display withdrawal symptoms. However, these are not exclusively related to its opioid effects and may reflect withdrawal from catecholamine and serotonin receptors and present as atypical sequalae. It is thus possible that acute dosing regimens are not sufficient to produce pronounced opioid-like effects but that a sustained high-dosing regimen of tramadol or tramadol abuse results in the development of neural adaptations characteristic of dependence for other mu-agonists.

Abuse potential

Functional magnetic resonance imaging (fMRI) used to study the effects of tramadol on the reward system in humans to assess drug abuse has shown several brain regions including nucleus accumbens (NAc) were activated during gain anticipation in the MID task under both tramadol and placebo. It was concluded that tramadol enhances the reward system and has the potential to precipitate drug abuse in humans.

Therapeutic applications / usefulness

A role for tramadol in the relief of various pain conditions including osteoarthritis, neuropathic pain, refractory restless leg syndrome, chronic low backache, cancer pain, and postoperative pain has been suggested. However, there is limited and low-quality evidence of the effectiveness of tramadol for these purposes. Therefore, it is unclear whether tramadol medication is efficacious or how it compares to morphine for pain relief.

Listing on WHO Model List of Essential Medicines
Tramadol is not listed on the WHO Model List of Essential Medicines.

Marketing authorizations
Marketing authorisations for tramadol as a medicine are held by many companies internationally. 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), as immediate- and extended-release formulations and for once-a-day (OD) dosing described variously as 'controlled', 'sustained', or 'delayed' release.

Industrial use
Industrial use of tramadol is not reported

Non-medical use
Epidemiological studies in the past have reported a lower tendency for tramadol misuse when compared to other opioids and therefore assumptions were made that its use would be less likely to be associated with diversion. However, new information indicates a growing number of tramadol misusers in some Middle Eastern and African countries, where diversion is a predominant source of the drug.

Nature and magnitude of public health problems
Tramadol is part of the response worldwide and is used to treat a wide spectrum of non-oncological pain conditions, as well as cancer pain. However, there is growing evidence that the adverse effects of tramadol are consistent with the adverse effects associated with other opioids. Abuse, dependence and overdose of tramadol have become a serious public health concern in some African countries and parts of Western Asia.

Licit production, consumption, and international trade
Available globally in tablet, capsule or injectable solution, tramadol is imported by many countries as the finished pharmaceutical product or directly in the powder form and pressed into tablets locally.

Illicit manufacture and traffic
Tramadol is available as an unbranded product often containing supra-therapeutic doses (up to 500 mg in some cases), and as a counterfeit medicine. In 2016, the International Narcotics Control Board (INCB) reported that over 40 million pills of counterfeit tramadol had been seized at the port of Cotonou, Benin, West Africa. Data provided by UNODC (July 2017) on global tramadol traffic showed a steady increase in seizures between 2007 and 2015. In 2012, the Container Control Programme (CCP) led to the seizure of 19 containers

with over 100 tons of fake Tramadol, all originating in India and seized in West Africa. At the end of 2017 the UNODC warned of the increase in trafficking and consumption of tramadol. In the last 5 years seizures of the drug have risen from 300 kg to more than 3 tonnes. Benin, Nigeria, Ghana, Togo, Niger, Sierra Leone, Cameroon and Cote d'Ivoire were highlighted as the major transit or destination countries. The involvement of criminal organisations, armed groups and terrorist organisations such as Boko Haram in Nigeria and the Islamic State of Iraq and the Levant in Libya have led to suggestions that the trafficking of tramadol plays a direct role in destabilising the region (World Report, May 2018).

Current international controls and their impact
Tramadol is not under international control

Current and past national controls
Tramadol is under national control in several countries

Substance identification

A. International Non-proprietary Name (INN)

Tramadol

B. Chemical Abstract Service (CAS) Registry Number

CAS-27203-92-5 (base)
CAS-36282-47-0 (hydrochloride salt)
CAS-22204-88-2 (hydrochloride salt)

C. Other Chemical Names

(±)-cis-(2-dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol
Or
(IRS, 2RS)-2-(dimethylaminomethyl)-1-(*m*-methoxyphenyl)cyclohexanol

D. Trade Names (including combinational medicinal products)

The following trade names have been listed (1,2):
Acema, Actidol, Acty, Acugesic, Adamon, Admadol, Adolonta, Altadol, Amadol, Amanda, Amdol, Ammitran, An-Tian, Ana-Q, Anadol, Analab, Analtram, Anangor, Anatram, Andalpha, 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, Combitram, 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, Esgipyrin, 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, Mobiya, 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, Oxxalgan, Ozitram, Pacmadol, Painadol, Paindol, 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, Traflash, 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 [2, 3]

E. Street Names

Chill Pills, Tramal Lite, Trammies, Ultras (https://www.thetreatmentcenter.com/resources/drug-slang/). Tablets of the Super Tramadol-X 200 brand are known in Cameroon as 'tomatoes' because of their packaging [4], as shown below.

Figure 1. Tramadol-225 mg (apple) and Super Tramadol -X 200 tablets (strawberry) as sold on the street in Cameroon [4].

In the Gabonese Republic, a country on the west coast of Central Africa tramadol goes by the name of 'kobolo' and is reported to be easily available on the streets of its capital Libreville (Figure 2). It is also known as the 'little red', 'pink baby' or 'kemeka', and tablets are sold for between 250 and 500 CFA francs (0.40 to 0.80 euros / $0.50 to $1.00) each. (Pulse News Agency International 05.02.2018, https://www.pulse.ng/bi/lifestyle/painkiller-nicknamed-kobolo-sparks-fears-for-gabons-young-id7935858.html)

Figure 2. Tramadol-225 mg known locally in Gabon as Kobolo (https://www.gaboninitiatives.com/trois-eleves-sanctionnes-detention-kobolo-minvoul/)

F. Physical Appearance (Colour, taste, smell)

Tramadol hydrochloride is a white, bitter, crystalline and odourless powder soluble in water and ethanol.

G. WHO Review History

Tramadol was pre-reviewed for the first time at the 28th meeting of the Expert Committee on Drug Dependence (ECDD) in 1992. The ECDD did not recommend critical review at the time based on 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 ECDD noted significant numbers of cases of the presentation of a withdrawal syndrome and adverse drug reactions, as well as its potential to produce morphine type dependence and recommended a critical review.

At its 33rd meeting in 2002, the Committee decided that the information presented in the review was not sufficient to recommend international control of tramadol but was adequate to recommend that the WHO keep the drug under surveillance.

Tramadol was pre-reviewed again at the 34th meeting in 2006 and it was noted that tramadol continued to show low level abuse potential, even following the major increase in the extent of its therapeutic use. The ECDD concluded that there was not sufficient evidence to justify a critical review.

The ECDD reviewed tramadol at its 36th meeting in 2014 and based on the evidence available recommended that a critical review of tramadol was not warranted at that time. However, a pre-review of tramadol was agreed based on information received by the WHO Secretariat regarding the misuse of tramadol [3].

In 2017 Tramadol was pre-reviewed at the 39th ECDD meeting (November 2017) and it was recommended that tramadol be subject to a critical review at a future meeting.

Chemistry

A. Chemical Name (IUPAC Name: CA Index Name)

The chemical name of tramadol hydrochloride is (±) c/s-2-((dimethylamino) methyl)- l-(3-methoxyphenyl)-cyclohexanol hydrochloride.

1RS,2RS)-2-(dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexanol

1RS,2RS)-2-(dimethylaminomethyl)-1-(m-methoxyphenyl)cyclohexanol

IUPAC Name: tramadol

CA Index Name: tramadol

B. Chemical Structure (Free base, Molecular Formula; Molecular weight)

Tramadol hydrochloride has a molecular formula of C16H25NO2 HC1 with a molecular weight of 299.84 (Figure 3).

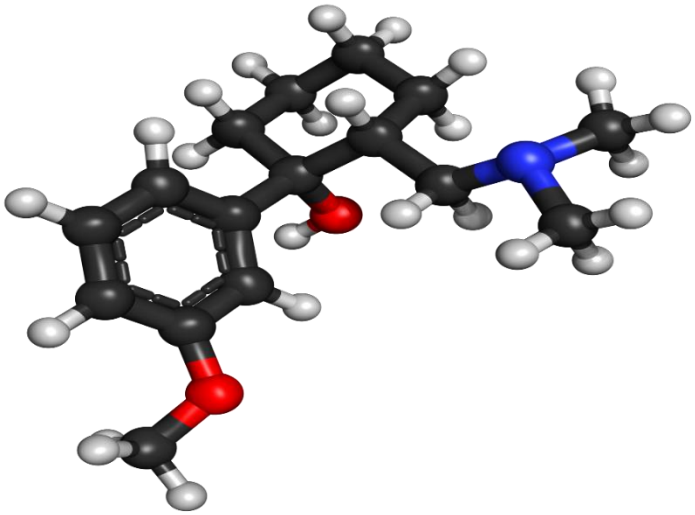


Figure 3. Three-dimensional representation of a Tramadol molecule (Image Jovan Gec, wiki/Tramadol#/media/File: Tramadol_3D.png/ 2018)

C. Stereoisomers

Tramadol can exist as different isomeric forms because of its chemical structure and has two chiral centres in the cyclohexane ring. Thus, four different stereoisomers exist: (1R,2R), (1S,2S), (1R,2S), and the (1S,2R) stereoisomer (Figure 4).

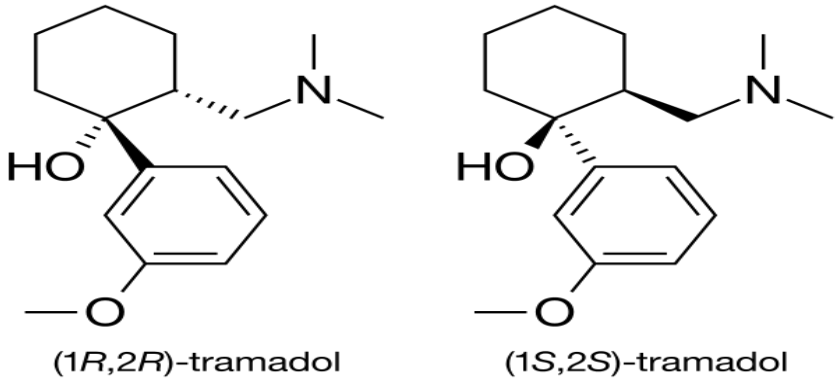


Figure 4 The stereoisomers of Tramadol (1R,2R), (1S,2S) (Vaccinationist, 2018, https://commons.wikimedia.org/w/index.php?curid=31174482/)

In the scientific literature different prefixes have been used (dextro, levo, d, l, R, S, cis, trans, erythro, threo, (+), (-)) to designate chirality and these may include combinations of these

prefixes sometimes with numerical designations. However, using a prefix to identify an isomeric form in the name does not alter the chemical structure of the drug. Hence tramadol remains 2-((dimethylamine)-mefhyl)- l-(3-methoxyphenyl)-cyclohexano.

The (R)-tramadol stereoisomer is a potent serotonin reuptake inhibitor, whereas the (S)-tramadol stereoisomer is a potent noradrenaline and serotonin reuptake inhibitor [5]. By independently enhancing noradrenergic and serotonergic activity, they work together to produce analgesic effects [6]. There are also some stereoisomeric differences in analgesic potency of the metabolite M1, with the (R)-O-desmethyltramadol configuration about 100 times more potent than that of the (S) configuration [7, 8].

Commercially available tramadol contains the racemic (1:1) mixture of the (1R,2R) and the (1S,2S) stereoisomers, also designated as the (R) or (+) and the (S) or (-) stereoisomer of cis-(2-dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexanol, respectively. The (1R,2R) and (1S,2S) stereoisomer have the hydroxyl and diethylaminomethyl group in cis-configuration55, and the methoxyphenyl group and the diethylaminomethyl group in transconfiguration (Figure 4).

D. Methods and Ease of Illicit Manufacturing

Tramadol was first synthesized in 1962 by Grünenthal GmbH in Germany by coupling cyclohexanon with 3-methoxyphenyl magnesium bromide in a Grignard reaction [1]. 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].

Illicit manufacture of tramadol appears to be well developed. Through its technical assistance programmes, the United Nations Office on Drugs and Crime (UNODC) and the World Customs Organization launched the Container Control Programme (CCP). In 2012 the programme led to the seizure of 19 containers with over 100 tons of fake tramadol, all originating in India and seized in West Africa [9].

In 2016 the International Narcotics Control Board (INCB) reported that the Control Unit at the port of Cotonu, Benin, West Africa had seized over 40 million pills of counterfeit tramadol. Increased misuse of tramadol was observed in the Sahel region and seems to have increased in Libya, which is considered a major source of tramadol trafficked to Egypt [10]. It has become clear that tramadol is not only diverted from legitimate sources (prescribing doctors or pharmacists) but from illicit trafficking of illegally manufactured tramadol and/or other substances sold pertaining to be tramadol mainly from China and India [11].

E. Chemical Properties

Molecular Formula:	C16H25NO2
Molecular Weight:	263.4 (base); 299.8 (hydrochloride salt)
Melting point:	hydrochloride salt: 180-181 °C
Boiling point:	388.1±22.0 °C at 760 mmHg
Density:	1.0±0.1 g/cm
Index of Refraction :	1.533
Solubility:	hydrochloride salt is readily soluble in water and methanol, slightly soluble in acetone and petroleum ether.
Dissociation Constant:	pKa 8.3, 9.41
Log partition coefficient:	Log P (octanol-water) 3.01, 1.35 at pH 7
Ultraviolet Spectrum:	Aqueous acid 272 nm: shoulder 279 nm
Infra-red Spectrum:	Principle peaks at wavenumbers 1284, 1601, 1042, 1238, 1575, 702 cm^{-1} [12]

F. Identification and Analysis (chemical spot tests, immunoassays, mass spectrometry, chromatography)

Tramadol can be identified in a variety of different matrices using chromatographic techniques. For instance:

- Gas Chromatography-Mass Spectrometry (GC-MS) without derivatization was used for the determination of tramadol and its metabolites in blood samples from tramadol-related deaths and four nonfatal intoxications. Blood concentrations ranging from 0.03 to 22.59 mg/L for tramadol, from 0.02 to 1.84 mg/L for 0-desmethly tramadol and from 0.01 to 2.08 mg/L for N-desmethyltramadol [13].
- Hair has become an important biomarker owing to the possibility of detecting target analytes for periods >1 month. A liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was developed for the quantitation of tramadol and its main metabolites in hair. The Lower Limit of Quantitation (LLOQ) values were in the range 0.010-0.030 ng/mg hair. The concentration of tramadol, 0- and N- desmethyl metabolites (M1 and M2) were markedly higher in the abuse cases (63.4-107.3 ng/mg, 3.8-6.3 ng/mg, 24.9-45.7 ng/mg hair, respectively) compared to non-abuse cases (3.3-20.1 ng/mg, 0.3-1.9 ng/mg, 0.5-4.3 ng/mg, respectively); also the values of N-desmethyltramadol/0-desmethly tramadol (NMDT/ODMT) ratio differed significantly. Binge patterns of use may influence the metabolites to parent drug concentration ratios and this parameter could represent a tool to identify abuse cases [14]
- Tramadol can be detected using preliminary urine drug screen tests (e.g., Abon Biopharm Multi-Drug Screen and Sure Screen Diagnostics) as well as automated immunoassay (e.g., ARCHITECT immunoassay analysing system) systems: commonly with a 300 ng/mL cut-off value [15, 16].

- Tramadol and its main metabolites M1 and M2 and O,N-di desmethyltramadol (M5) have also been determined simultaneously in human plasma, oral fluid and urine by High Performance Liquid Chromatography (HPLC). A Chromolith Performance RP-18e 100 mm x 4.6 mm column was employed with fluorescence detection (301 nm). The lower limit of quantification (LLQ) was 2.5 ng/mL for all compounds. The assay was applied to assess the pharmacokinetics of tramadol and its main metabolites following administration of a single oral dose (100 mg) tramadol to healthy volunteers [17].
- The stereoisomers of tramadol have been detected using a maltodextrin-modified capillary electrophoresis method for a single-run chiral separation of tramadol and was reported with detection limits of 2 $\mu g\ mL^{-1}$. This method was successfully applied to the measurement of drug concentrations in tablets, urine, and plasma samples [18].
- HPLC (linear dual column -MS/MS) has also been used for the simultaneous determination of tramadol and its O-desmethyltramadol metabolite, N-desmethyltramadol (M2) and N,O-didesmethyltramadol metabolites in oral fluid [19].

In Croatia, raw wastewater, secondary effluent and river water were analysed by reversed-phase liquid chromatography using a Synergy Polar column coupled to electrospray ionization tandem mass spectrometry (LC-MS/MS). The concentrations of individual opioid analgesics in municipal wastewater varied from < 0.2 to 859 ng/L: tramadol was one of the most prevalent compounds present [20].

Ease of convertibility into Controlled Substances

Tramadol is not likely to be converted into a controlled substance

General Pharmacology

Tramadol is well known as an analgesic that produces opioid-like effects primarily due to its metabolite, O-desmethyltramadol (M1). The analgesic effect of tramadol involves both opioid and noradrenaline and serotonin receptor systems. The production of analgesia is consistent with M1 formation, which commences an hour post-administration and peaks 2 to 3 hours later.

Tramadol has some affinity for the μ-opioid receptor whereas the active hepatic metabolite, M1 has high relative intrinsic efficacy and greater affinity for the μ-opioid receptor [21] [22]. The affinity of morphine (schedule C-II, USA) is approximately 10-100 times greater than M1 and 300 times greater than tramadol. Tramadol is approximately 10-fold less potent than codeine (schedule C-II, USA), 1000-fold weaker than methadone (schedule C-II, USA), and 6000-fold weaker than morphine (schedule C-II, USA) [23]. The

analgesic potency of tramadol is about 10% that of morphine following parenteral administration [24] but more potent if administered orally because of the activity of M1.

It is well established that both tramadol and M1 inhibit the reuptake of serotonin and noradrenaline. Hence, the concomitant use of serotonergic drugs such as serotonin re-uptake inhibitors and monoamine oxidase inhibitors (MAOIs), increase the risk of adverse events, including seizure and serotonin syndrome. Tramadol has 2 chiral centres, (R) and (S) tramadol. The effect of noradrenaline and 5-HT reuptake and 5-HT release is thought to be mainly mediated by the parent compounds with (S) tramadol being 5-fold more potent in inhibiting noradrenaline than inhibiting 5-HT reuptake and the reverse for (R) tramadol. The monoaminergic component of analgesia is thought to be mediated by (R) and (S) tramadol [25]. Recent evidence suggests that tramadol is only contraindicated in combination with MAOIs but no other antidepressants in common use today [26].

Tramadol causes respiratory depression in a dose dependent manner in laboratory animals, but this activity is only partially blocked by naloxone: both monoaminergic and opioid mechanisms contribute to this effect. Scott and Perry, 2000 [27] report that unlike other opioids, tramadol has no clinically relevant effects on respiratory or cardiovascular parameters at recommended doses in adults or children. In a case series study of tramadol overdose (N = 71: median age: 41 years, range: 17-69 years; and median ingested dose: 1000 mg), respiratory depression occurred in 13, median dose: 2500 (IQR: 1600-3000) mg, which was significantly different (p = 0.003) to patients without respiratory depression, median dose: 1000 (IQR: 750-1475) mg. Respiratory depression occurs only in severe cases of overdose with very high doses [28].

A comparison of tramadol and tapentadol exposures reported to the Data System of the American Association of Poison Control Centres between 2009 and 2014 revealed that individuals exposed to tramadol (8566 cases) identified significantly higher rates of seizures and vomiting, whereas tapentadol was associated with more classical opioid agonist effects such as respiratory depression [29, 30]. A study in Iran found that generalized seizures were reported to occur within the first 24 hours after administration [31], although isolated idiosyncratic cases have been reported [32]. Thus, tramadol acts in a multimodal fashion to bring about analgesia that involves both the μ-opioid receptor system, the nor adrenergic system and the serotonergic system [3].

The pharmacological properties of this dual opioidergic and monoaminergic drug may also be modified because of cytochrome (CYP) P450 enzyme modulation by drug interactions and/or genetic polymorphisms. In CYP2D6 poor metabolisers (PMs), tramadol properties will move towards a monoaminergic antidepressant-like molecule devoid of opioidergic activity, whereas the opioidergic properties will be more pronounced in CYP2D6 ultra-rapid metabolisers (UM). Different pharmacological effects can therefore be expected depending on an individual's CYP2D6 phenotype [33]. The importance of these pharmacogenetic modulations and/or drug interactions needs to be further investigated not only in the clinical setting but also in those misusing the drug [34].

A. Routes of Administration and dosage

In the United States, ULTRAM (tramadol HCL) was approved by the Food and Drug Administration in 1994 as a non-scheduled drug under the Controlled Substance Act. Tramadol HCl tablets (generic ULTRAM, 50 mg) are marketed by Amneal Pharmaceuticals as shown in Figure 5.

Figure 5 shows an image of generic ULTRAM (Rotellami1,2018)

Tramadol is marketed as the hydrochloride salt and is available in a variety of pharmaceutical formulations for oral (tablets, capsules), sublingual (drops), intranasal (spray), rectal (suppositories), intravenous, subcutaneous, and intramuscular administration. It is also available in combination with acetaminophen (paracetamol), immediate-release and extended-release formulations. The following pharmaceutical formulations are available for oral use: 50 mg immediate-release (IM) tablets/capsules; 50 mg; 100 mg; 150 mg; 200 mg; and 300 mg extended-release or sustained-release (SR) tablets/ capsules and 37.5 mg tramadol + 325 mg acetaminophen tablets/capsules.

Globally, tablets and capsules are the most commonly used and easily available formulations. The recommended daily dose is in the range of 100-400 mg and the maximum dose should not exceed 400 mg per day. Immediate release formulations may be given every 4-6 hours and extended-release every 12-24 hours. Sustained-release tablets liberate the active ingredient over a period of 12 hours. Starting treatment with tramadol SR capsules at a dosage of 50 mg twice daily with subsequent dose escalation resulted in improved tolerability in patients (N= 3888) with moderate to severe chronic pain. The lowest tramadol SR capsule dosage of 50 mg twice daily (administered to 35% of patients with moderate to severe non-oncological pain) significantly improved pain intensity and frequency in 83.4% and 70.4% of patients, respectively [35]. Certain products such as secure-release formulations of once-a-day (OD) tramadol have been developed to prevent abuse by the inhalational route [36, 37], although this does not appear to be the predominant route of administration.

Newer slow release formulations have used biotechnology to establish alternative liberation characteristics for tramadol. Despite being described as OD these preparations often have different release profiles. For instance, comparison of three 200 mg OD tramadol formulations (200 mg SMB Technology, Belgium; Zambon 200 mg, Spain and Contramid® Labopharm, Canada) showed significant differences. With SMB tramadol a lag period occurred after ingestion during which no appreciable drug absorption took place: the maximum plasma concentration occurring >10 hours later. This formulation was confirmed as a “delayed-release” formulation, whereas the other two (Zambon and Labopharm)

showed consistent release following administration and pharmacokinetics characteristics of "controlled-release" [38].

Co-crystal technology, a new alternative pharmaceutical approach described as either a multicomponent drug or a multimodal agent [39] incorporates two different active pharmaceutical ingredients (APIs) in the same crystal lattice. Almansa et al, (2017) described tramadol hydrochloride−celecoxib (CTC; E-58425/MR308) as a pharmaceutical co-crystal. Tramadol-celecoxib (CTC) was a first-in-class active pharmaceutical ingredient (API-API) co-crystal of racemic tramadol HCl and celecoxib in a 1:1 molecular ratio (100 mg CTC: 44 mg racemic tramadol HCl and 56 mg celecoxib) [40]. This novel formulation has been reported to display favourable physicochemical and dissolution profiles [39].

B. Pharmacokinetics

After oral administration tramadol is rapidly and almost completely absorbed (with a time lag of 30 minutes for capsules). Peak plasma concentration occurs about 1.6–1.9 h after oral administration of immediate release formulations [41]. The bioavailability of tramadol is around 70% after single dose administration, but increases to 90%–100% after repeated administration as a result of the saturation of the hepatic first pass effect [27]. Tramadol SR capsules had identical bioavailability to tramadol immediate-release (IR) capsules with lower peak concentrations and less fluctuation in plasma concentrations. Tramadol SR 100 mg capsules administered twice daily had equivalent efficacy to tramadol IR 50 mg capsules administered four times daily [35].

Tramadol is mainly metabolized by two pathways: N- and O-demethylation (phase I reactions) and conjugation (phase-II reactions). There are at least 11 known metabolites of tramadol (M1 to M5 and glucuronides and sulfates of M1, M4, and M5). The metabolites M2, M3 and M4 of tramadol have negligible affinity for the human μ-opioid receptor. The O-demethylation of tramadol to M1, the main analgesic effective metabolite, is catalysed by cytochrome P450 (CYP) 2D6, whereas N-demethylation to M2 is catalysed by CYP2B6 and CYP3A4 (Figure 6).

The wide variability in the pharmacokinetic properties of tramadol can partly be ascribed to cytochrome P450 polymorphism. O- and N-demethylation of tramadol as well as renal elimination are stereoselective. Pharmacokinetic-pharmacodynamic characterisation of tramadol has been complicated because of pharmacodynamic interactions between the two stereoisomers of tramadol and its active metabolites [24].

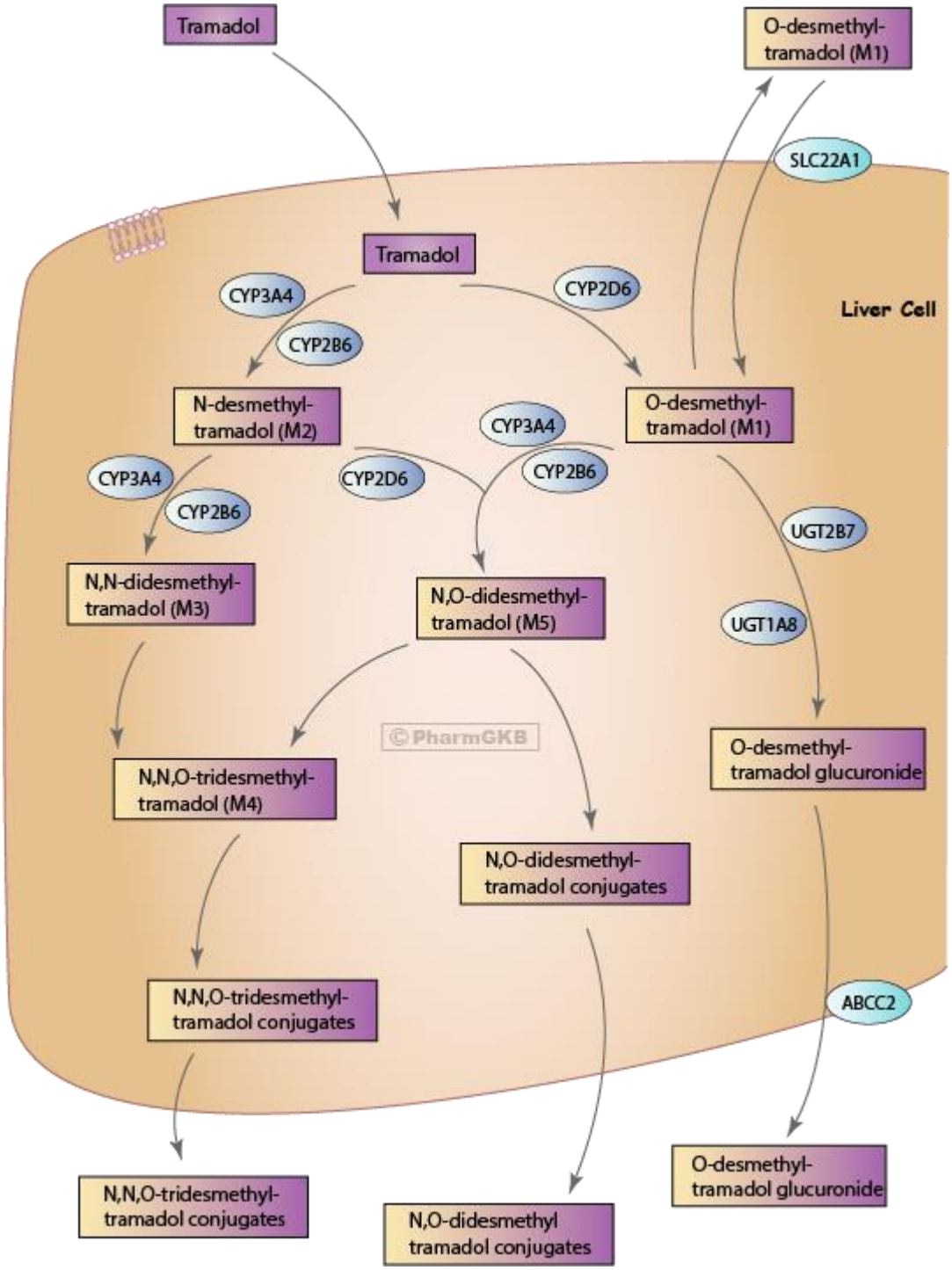


Figure 6 Metabolic routes of tramadol and its main metabolites O-desmethyltramadol (M1) and N,O-desmethyltramadol (M5) in the liver (PharmGKB, https://www.pharmgkb.org/pathway/PA165946349).

The phenotypic status of an individual may affect the therapeutic response. The plasma concentrations of both tramadol stereoisomers were found to be considerably higher in Poor Metabolizers (PM) than in Extensive Metabolizers (EM), resulting in 43% and 37% increase in area under the plasma concentration curve (AUC) values of (R)-tramadol and (S)-tramadol respectively.

The mean peak plasma concentration of M1 occurs after about three hours in healthy adults. The organic cation transporter 1 (OCT 1) facilitates the uptake of tramadol into hepatocytes for metabolism. Volunteers carrying loss-of-function OCT1 polymorphisms had significantly higher plasma concentrations of O-desmethyltramadol (P = 0.002, n = 41) and significantly prolonged miosis, a surrogate marker of opioidergic effects (P = 0.005, n = 24) [42]. It is of note that the activation of tramadol takes place independently of OCT1, and thus, the accumulation of metabolites can still occur based on variations in the transporter [43].

The FDA-approved drug label for tramadol reports concentrations of tramadol were approximately 20% higher in PM versus EM, while M1 concentrations were 40% lower. The label also states that other factors, such as the concurrent use of CYP2D6 inhibitors (e.g., fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine) could also result in increases in tramadol concentrations and decreased concentrations of M1. It was also noted that the impact of these drug-drug interactions in terms of either efficacy or safety is unknown [44].

The plasma concentrations of the (R)- and (S)-M1 stereoisomers in EMs were significantly higher than the respective concentrations in PMs following administration of a 100 mg single oral dose of racemic tramadol to 24 male and female subjects. Although the concentration profiles and most of the calculated pharmacokinetic parameters of tramadol and its main metabolites appear to be different in EMs and PMs, only the stereoselectivity of M1 enantiomers was significantly different in relation to CYP2D6 subgroups, suggesting that some observations may be transient. No significant gender-related difference in the pharmacokinetics of tramadol and its metabolites was observed [45].

Significant interethnic differences in CYP2D6 allele frequencies have been demonstrated across many countries. For instance, the carriers of gene duplications or multi-duplications are assigned to the ultra-rapid metaboliser (UMs) phenotype. UMs are more prevalent in the Southern European countries (Spain 7–10 %, Sicily 10 % and Sweden 1–2 %). Gene duplications are described in 20 % of Saudi Arabians and 29 % of Ethiopians [34]: the UM phenotype is most common in eastern Africa [46]. Administration of standard doses of CYP2D6-metabolized drugs to UM individuals may result in therapeutic failure because of a low plasma concentrations of active drug/ metabolite [47] or conversely, may lead to supratherapeutic concentrations of active metabolite formation and potentially serious side effects [48].

The prevalence of the PM phenotype is slightly higher among Asians in the Indian subcontinent than in the Asian populations of south-eastern and eastern Asia, with frequencies of 1.8%–4.8% reported [49]. CYP2D6*10 may be present in as many as 50% of Asians and is responsible for diminished enzyme activity in intermediate metabolisers (IMs) [50]. Reports on the prevalence of PMs in African populations differ widely, with estimates varying in the range of 0%–19% [51]. The CYP2D6*17 allele which encodes the enzyme with lower catalytic function was found at a frequency of 26% among the Ghanaian population [52, 53].

The following table provides estimates of the prevalence of ultra-rapid metabolisers (UM) of CYP2D6 in different populations (Table 1). Further information can be found from the electronic Medicines Compendium (eMC), which provides information about medicines licensed for use in the UK (*https://www.medicines.org.uk/emc/ product/ 5924/ smpc).* The eMC is vetted by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA).

Table 1 estimates of the prevalence of ultra-rapid metabolisers (UM) of CYP2D6 in different populations [34]

Population	Prevalence (%)
African/Ethiopian	29%
Saudi Arabians	20%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

There seems to be sufficient evidence to support the use of widespread genetic screening to predict individual responses to opioid pain medications and the risk of adverse events. Although available, there is some evidence that healthcare professionals do not organise such tests possibly because they are cost-prohibitive in some settings. It may be that if such tests become part of standard clinical practice for tramadol the efficacy of this drug would be clarified.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. The relationship between serum concentrations and the analgesic effect is dose-dependent but varies considerably in isolated cases. A serum concentration of 100 - 300 ng/ml is usually effective. However, pharmacokinetic profiles have been reported to differ according to the liberation characteristics of different formulations.

Significant differences in pharmacokinetic parameters were observed when 200 mg OD tramadol formulations (Zambon, Spain and Contramid Labopharm, Canada) were compared with tramadol Contramid® ($p < 0.0004$), displaying a significantly shorter elimination half-life (7.4 vs 14.9 h, $p = 0.0001$). Oral administration of tramadol Contramid® led to mean plasma concentrations maintained at a plateau above 200 ng/mL for ≥12h (4 h - 16 h post-dosing), while plasma concentrations were maintained for only 2 h with tramadol Zambon (4 h - 6 h post dose). Mean plasma concentrations of tramadol at 24 h were significantly higher after tramadol Conradmid® administration (38.9 vs 26.2 ng/ml $p = 0.0001$). These formulations were not considered bioequivalent [38]. When compared to a hydrophilic OD tramadol formulation (200 mg, SMB Technology, Belgium), the following values were observed for time to reach peak plasma concentration (T_{max}): OD tramadol Contramid® (Labopharm) 9.0 h (2–16 h), OD tramadol (Zambon) 4.5 h (2–12), and OD tramadol (SMB Technology) 10 h (6–12) [38]. It is unclear whether the differences in these formulations are widely known in clinical settings or the extent to which they are abused.

The volume of distribution of tramadol has been reported to be 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The plasma binding of tramadol is approximately 20% and the binding capability appears to be independent of concentration up to 10 pg/mL [38].

Tramadol crosses the blood–placental barrier and a very small amount of the drug is excreted in breast milk [37]. No significant behavioural adverse effects have been reported in neonates exposed to tramadol and short-term maternal use of tramadol during establishment of lactation has been reported to be compatible with breastfeeding [54].

Tramadol is mainly excreted through the kidneys and the rest through the fecal route [41, 45]. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% is excreted as metabolites. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 have been reported to be between 5 and 6 hours and about 7 hours respectively [24, 27, 45]. The mean half-life of tramadol in overdose has been reported to be 9.24 hours [55], which suggests that the metabolism of tramadol is capacity limited and dependent upon the rate at which the drug can be metabolised by the P450 enzyme system.

Summary of PK characteristics of tramadol [12]

Bioavailability	– 70% (to 100% with continued dosing)
Plasma elimination half-life	– 6h (increase to 7 with multiple dosing)
	– 7h (M1 metabolite)
Volume of distribution	– 3 L/Kg
Clearance	– 6mL/min/Kg
Plasma binding	– 20%
Therapeutic concentration	– 100 – 800 µg/L
Toxic tramadol concentration	– 1mg/L
Lethal tramadol concentration	–2mg/L

C. Pharmacodynamics

Tramadol produces its analgesic effects largely by opioid mechanisms. Tramadol has a weak affinity for the µ-opioid receptors (encoded by gene OPRM1) through the parent drug and the primary O-desmethyltramadol (M1). The µ-opioid receptor agonistic activity of tramadol is almost 6000-fold less than that of morphine. However, its metabolite, M1 has 300 times more affinity for the mµ receptor as compared to the parent compound of tramadol. Tramadol also displays a weak agonistic effect at the δ-opioid receptors and a weaker affinity for κ-opioid receptors [24].

The other mechanisms by which tramadol acts on the central nervous system includes monoaminergic activity through weak inhibition of noradrenaline and serotonin reuptake by the parent drug to enhance inhibitory effects on pain transmission [56]. In early reports (1996 and 2001), tramadol-induced analgesia was reported to be only partly antagonised by

the opioid antagonist naloxone, but evidence was limited to yohimbine a α2-adrenoreceptor antagonist [57], and the selective 5-HT3 receptor antagonist, ondansetron [58]. In the latter case, dosage increases may have been more to do with antiemetic effects than the need to address insufficient pain relief.

Concomitant use of serotonergic drugs such as serotonin re-uptake inhibitors (SRIs) and monoamine oxidase inhibitor inhibitors (MAOIs) may enhance the risk of adverse events, including seizure and serotonin syndrome. Concomitant use of tramadol with carbamazepine, digoxin, erythromycin, ketoconazole, lithium, mirtazapine, bupropion, fluoxetine, paroxetine, phenytoin, promethazine, rifampicin, ritonavir, quinidine, trazodone, coumarins, diuretics, phenothiazines, and triptan medicines should therefore be undertaken with care. No significant drug interactions were observed between pregabalin and tramadol, with 90% CI of pharmacokinetic measures within the conventional bioequivalence range [59].

CYP2D6 ultra-rapid metabolisers (UM) have been reported to be more likely to experience adverse effects from tramadol than other phenotypes and it has been recommended that in individuals with this phenotype opioid analgesics that do not rely on CYP2D6 should be used for therapeutic activity [60].

Clearly, no such checks are in place for UM individuals who misuse tramadol, although the risk of adverse event is likely to be greater because of high dose consumption. For example, high concentrations of both tramadol and its main metabolite O-desmethyltramadol were attributed to the refractory cardiac arrest of a 22-year-old Caucasian female admitted to hospital. Genotyping of CYP2D6 revealed the patient to be heterozygous for a duplicated wild-type allele, predictive of a CYP2D6 UM phenotype (later confirmed by analysis of the tramadol/ M1 metabolic ratio). The event was specifically ascribed to the inhibition of noradrenaline reuptake and excessive blood adrenaline levels following binge-type ingestion of tramadol (to gain a "high") that led to strong myocardial stunning [48].

Pharmacogenetics is a rapidly expanding field and there is currently sufficient evidence to support the use of widespread genetic screening to predict individual responses to pain medications and the risk of adverse events and should be encouraged as part of standard clinical practice for tramadol. Although available, there is some evidence that healthcare professionals do not organise phenotypic tests [61]. Knowledge of the phenotypic status of an individual may also help those who abuse the drug and help explain pockets of serious adverse events in some communities. Work has been done to suggest that CYP2D6 genetic variations may be studied in oral fluid since ratios of M1/tramadol, M2/tramadol and M5/M2 correlated well with the CYP2D6 genotypes [19]. Oral fluid tests may encourage healthcare professionals to use pharmacogenetic tools more often.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has recently published guidelines for opioid therapy (codeine) in the context of CYP2D6 phenotype [34, 62]. CPIC was established to provide drug-dosing guidelines based on an individual's genotype. These peer-reviewed gene–drug guidelines are published and updated periodically on the PharmGKB website (https://www.pharmgkb.org/). The authors strong recommendation

was to avoid codeine use in CYP2D6 UM and PM phenotypes and consider alternative analgesics. In 2011, the Dutch Pharmacogenetics Working Group Guideline edited the same recommendation to include tramadol [33].

Toxicology (acute and chronic preclinical and clinical toxicology)

Preclinical

Preclinical studies found that in animals with painful stimulation, tramadol demonstrated a dose-related anti-nociceptive effect. The animal models included tail-pressure, paw-pressure, and electrically induced vocalization tests in rats; tail-flick, hot-plate, and abdominal constriction tests in mice and rats; and the electrical tooth-pulp stimulation test in rabbits. The intravenous administration of either tramadol or M1 produced dose-dependent analgesia and the following descending order of analgesic activity was found: hydromorphone > hydrocodone > morphine > M1 or codeine > tramadol [23].

Tramadol has been reported to impact spermatogenesis and disturbs reproductive hormones in animal studies. Electron microscopic (EM) examination showed ultrastructure alterations in a dose-dependent manner. Tramadol was concluded to adversely affect all epididymal cells, which subsequently deteriorate epididymal function and may affect sperm maturation, leading to subfertility [63]. Administration of tramadol to male albino rats led to histological abnormalities on both cerebral cortex and testicular tissues associated with oxidative stress in these organs. There was increased apoptosis in both organs which regresses with withdrawal. These findings may provide a possible explanation for delayed fertility and psychological changes associated with tramadol abuse [64].

On repeated oral and parenteral administration of tramadol in rats (for 6 - 26 weeks) and dogs and oral administration (for 12 months) haematological, clinical chemistry and histological investigations showed no evidence of any substance-related changes. It is noteworthy that central nervous manifestations only occurred after doses considerably above the therapeutic range were administered: restlessness, salivation, convulsions, and reduced weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and rectal doses of 20 mg/kg body weight in dogs without any reactions [65]. In dogs (R)-tramadol is metabolised in dog liver to (R)-M1 exclusively by CYP2D15 and to (R)-M2 by multiple CYPs, but primarily CYP2B11. (R)-M1 was potently inhibited by sulfaphenazole (CYP2C inhibitor) and chloramphenicol (CYP2B11 inhibitor) and was greatly increased in phenobarbital-treated dogs [66] suggesting enzyme modulations and drug-drug interactions are important variables in the efficacy of the drug .

In New Zealand male rabbits administered tramadol, overall changes in the concentrations and numbers of fatty acids were thought able to disrupt membrane fluidity of the blood brain barrier and possibly cause neurotoxicity [67]. The metabolism of tramadol induces oxidative stress in different organs in rodents. The hepatic and renal toxicities caused by tramadol in the rat were explored by investigating the changes in the activities and the protein expressions of CYPs isozymes (2E1, 3A4, 2B1/2), antioxidants status, free radical

levels after pre-treatment of rats with Curcumin and/or Gallic acid as single- and/or repeated-doses before administration of tramadol. Pre-treatment of rats with curcumin and/or Gallic acid prior to administration of tramadol restored the inhibited DMN-dl activity and its protein expression (CYP 2E1) to their normal levels [68].

Pfizer, in its marketing authorisation application for 50 mg capsules classified tramadol as non-mutagenic following studies on the tumorigenic potential of tramadol hydrochloride carried out in rats and mice https://mri.cts-mrp.eu/Human/ Downloads /PT_H0803_001 _FinalSPC.pdf).

Clinical

Few studies exist regarding the risk of a teratogenic effect of tramadol when used in early pregnancy. Using the Swedish Medical Birth Register, women (deliveries in 1997-2013) who had reported the use of tramadol in early pregnancy were identified. Maternal characteristics and concomitant drug use were analysed. Among 1,682,846 women (1,797,678 infants), 1751 women (1776 infants) had used tramadol, 96 of the infants had a congenital malformation and 70 of them were relatively severe. The adjusted odds ratio for a relatively severe malformation was 1.33 (95% CI 1.05-1.70). The odds ratios (ORs) for cardiovascular defects (1.56, 95% CI 1.04-2.29) and for pes equinovarus (3.63, 95% CI 1.61-6.89) were significantly increased. The study suggested a teratogenic effect of tramadol, but the risk increase is moderate [69].

Adverse Reactions in Humans (include acute and chronic physical and psychological effects)

Acute

Adverse effects associated with tramadol are well described and like those of other weak opioids. Common side effects include dizziness, nausea, constipation, and headache. In a study of tramadol overdose from seven U.S. poison centres over the period from October 1995 through August 1996, 126 cases of tramadol overdose presented multiple systematic symptoms ranging from cardiovascular toxicity to significant neurologic toxicity including lethargy, nausea, tachycardia, agitation, seizures, coma, hypertension and respiratory depression.

In a retrospective chart review of tramadol exposures reported to a multisite, state-wide poison control system over a 2.5-year period, 190 cases were considered. Acute ingestions represented most of cases (90.0%, 55% were females). Logistic regression analysis showed an association between seizures and tramadol use in males, chronic use, suicide attempts, intentional abuse or misuse, and tachycardia (HR >100 beats/min). Doses ranged from a taste amount to 5000 mg. The smallest amount of tramadol associated with a seizure was 200 mg, and 84.6% of seizures occurred within 6 hours of time of ingestion [70].

The mechanism underlying tramadol toxicity has been closely related to both its opioid receptor activity and its monoamine oxidase inhibitor (MAOI) activity [23, 71]. Acute toxicity resulting from excessive intra-synaptic serotonin (serotonin syndrome), is now understood to be an intra-synaptic serotonin concentration-related phenomenon. Recent research more clearly delineates serotonin toxicity as a discreet toxidrome characterised by clonus, hyper-reflexia, hyperthermia and agitation. It is only combinations of serotonergic drugs acting by different mechanisms that can raise intra-synaptic serotonin to a concentration that is life threatening. The combination that most commonly does this is a MAOI drug combined with any SRI [72]. Such events have been reported with tramadol [26, 73].

Based on the genetic differences and the ability to produce different ratios of (R) and (S) tramadol stereoisomers, it is possible that individual differences in plasma concentrations of (R)-O-desmethyltramadol and (S)-O-desmethyltramadol affect who develops serotonin syndrome. Although metabolic ratios are reported to be stable in an individual, inhibition or induction from concomitantly administered medications may increase or decrease the metabolic ratio, respectively. The relationship between genetically influenced tramadol metabolism and the impact on drug–drug interactions contributing to serotonin syndrome needs further delineation[26].

In countries were tramadol abuse has been reported as problematic, overdose has been reported to be disproportionately more common than overdose with other substances. For instance, in Iran tramadol overdose has become one of the most common causes of poisoning admissions to emergency departments in the country. A study of (N = 121, non-seizure group = 61 and seizure group = 60) tramadol users, mean age 25 yrs. were admitted to in hospitals in Ghaemshahr, Iran. Tramadol-induced seizures were not found to be related to age, gender, or dosage but led to cardiovascular and renal complications [74]. Use or abuse of supratherapeutic doses of tramadol are a known risk factor and if left untreated, morbidity and mortality can be high [75] .

Chronic

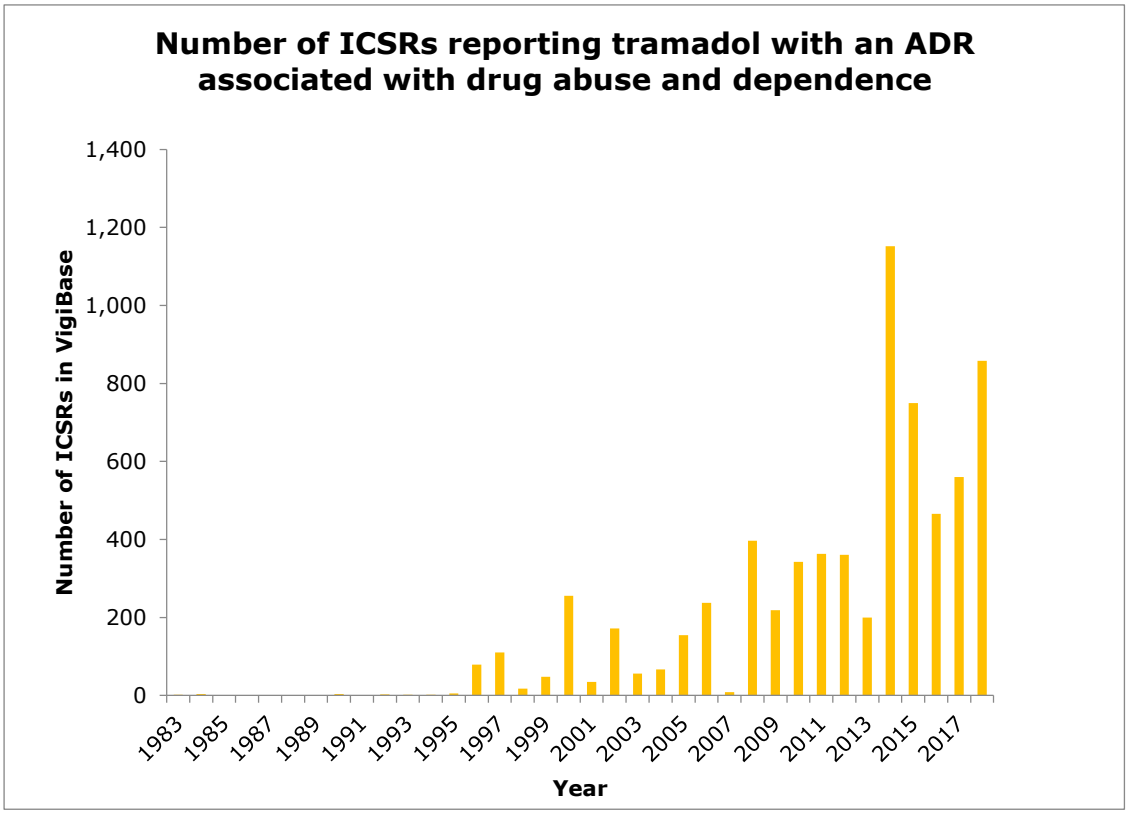
Chronic non-medical users of tramadol have been reported. They tend to have a history of dosage ingestion much higher than recommended for analgesia. In individuals reported to have ingested > 675 mg/day (three or more tablets of 225 mg) for longer than 5 years (N = 79) anger, hostility and aggressive behaviour were reported as commonplace. After treatment however, the main problem observed was the significant increase in comorbid anxiety, depressive, and obsessive-compulsive symptoms: there was no increase in psychotic symptoms [76]. Psychiatric co-morbidity has been reported in 100 Egyptian patients dependent on tramadol with approximately 3 out of 4 diagnosed with cluster B personality disorders [77].

In 2018, the International Narcotics Control Board (INCB) [78] reported widespread misconceptions regarding tramadol among the general population in North Africa and the Middle East . Some consider the drug to be a mood enhancer, whilst others consider it to increase sexual stamina or boost energy during work. However, mood elevation is often reported and leads to the consumption of higher doses of the drug, psychological or

physical dependence and increased risk of overdose. Symptoms of toxicity included coma, cardiac arrest, collapse and respiratory depression or arrest.

The WHO Global Database (VigiBase) reports of suspected adverse drug reactions (ADRs) also known as Individual Case Safety Reports (ICSRs) were studied to investigate tramadol (Figure 7).

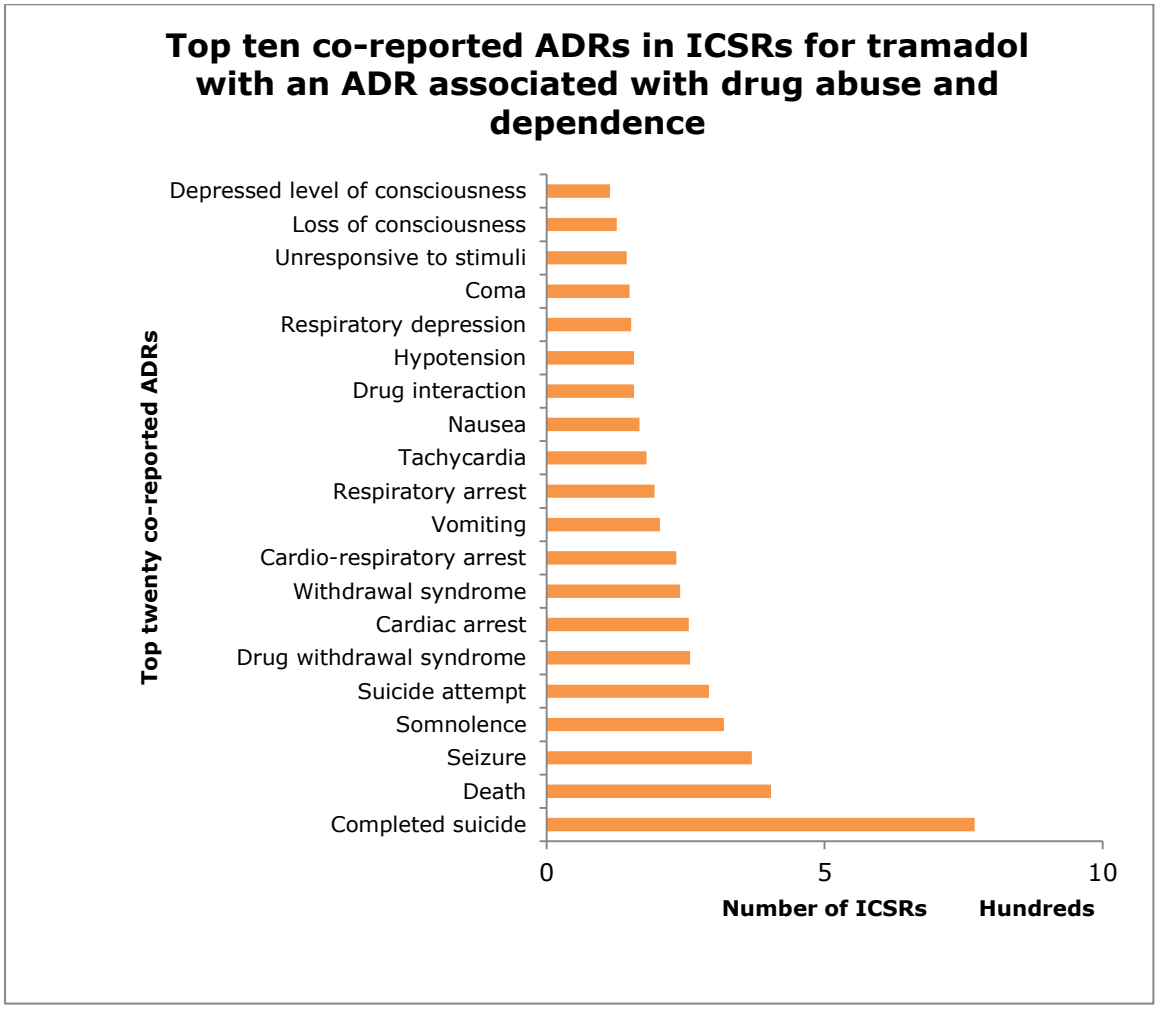
Figure 7 Number of ICSRs reporting tramadol with an ADR associated with drug abuse and dependence over time



Currently 131 countries contribute to VigiBase and there have been over 17 million ICSRs recorded. With regards to tramadol there were 6934 ICSRs reporting an ADR related to the abuse and dependence in VigiBase (1968-October 2018). The ICSRs originated from 46 countries, with the majority from the United States (69%): in Europe ICSRs were recorded for Germany (8%) and France (6%). There has been a sudden increase in reports (nearly 5-fold) for tramadol; from 200 ICSRs in 2013 to 1152 in 2014 (Figure 7).

The most commonly reported ADRs related to drug abuse and dependence were completed suicide, death, seizure, and somnolence (Figure 8) [79].

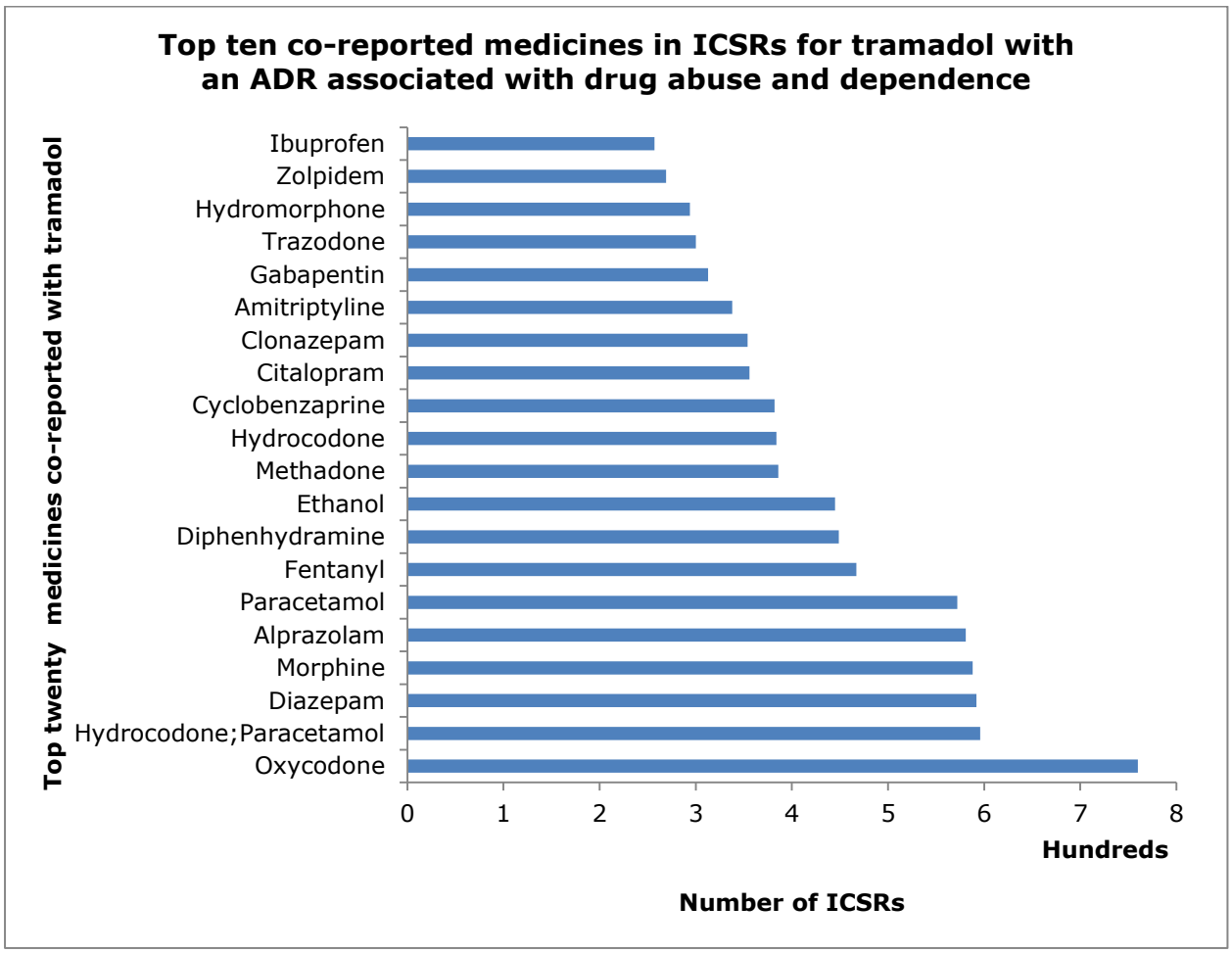
Figure 8 Top ten co-reported ADRs in ICSRs for tramadol with an ADR associated with drug abuse and dependence in VigiBase



Tramadol was commonly reported in suspected suicide poisonings and misuse poisonings in Ohio adolescents and young people between 18-24-year olds recorded in the Poison Control Centre (PCC) [80]. Medicines that were co-reported with tramadol included oxycodone, paracetamol, hydrocodone and diazepam (Figure 9) [79].

Serotonin syndrome is a potentially life-threatening syndrome that may occur with the use of tramadol, especially if other medications such as antidepressants that enhance serotonergic action or other drugs that impair the metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors) are used concurrently. Symptoms include changes in mental status (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea) [73].

Figure 9 Top ten co-reported medicines in ICSRs for tramadol with an ADR associated with drug abuse and dependence



Dependence Potential

A. Animal Studies

Animal studies on the abuse and dependence potential of tramadol may not be a reliable predictor of the human experience. Often animal studies and human trials can be substantially discordant, and researchers have identified major methodological limitations of animal research and its applicability to humans [81]. Various points have been raised that suggest caution should be exercised when extrapolating findings in animals to humans. Those pertinent to the discussion relating to tramadol include:

- Disparate animal species and strains, with a variety of metabolic pathways and drug metabolites, leading to variation in efficacy and toxicity (e.g., enzymes other than CYP2D6 involved);
- Variations in drug dosing schedules and regimens of uncertain relevance to the human condition (e.g., IV administration tramadol in animals not pertinent to oral use in humans);

- Variability in animals for study, methods of randomization, choice of comparison therapy (none, placebo, vehicle);
- Small experimental groups with inadequate statistical power; simple statistical analyses that do not account for confounding; and failure to follow intention-to-treat principles;
- Nuances in laboratory technique that may influence results, for example, methods for blinding investigators, being neither recognized nor reported [82].

This may be the reason why generally, the evidence reported about the dependence potential and abuse liability of tramadol as well as the effect on the dopaminergic and serotonergic systems of tramadol in animals has been inconsistent.

In some, rhesus monkeys for instance, only mild to moderate withdrawal symptoms were detected [83], although sedation and pruritus has been observed more recently after IV administration [84]. In rodents it was found that tramadol did not show any positive effects in climbing, jumping, and head-twitch tests but in the conditioned place preference and self-administration tests, the experimental animals showed significant positive responses. Taken together, it was concluded that tramadol affected neurological systems and had the potential to lead to psychological dependence [85] .

B. Human Studies

Tramadol dependence has been reported in Egypt since 2004. To evaluate the chronic sequelae of tramadol dependence, subjects with at least 5 years history of chronic use (>675 mg/day, 3 x 225 mg/day) were recruited (N=79). Whilst clinical chemistry was within normal parameters, subjects were described as angry, hostile, and aggressive. On cessation of dosing and detoxification there was a significant increase in comorbid anxiety, depressive, and obsessive-compulsive symptoms [76].

Dependent individuals are reported to display withdrawal symptoms, but these are not exclusively related to its opioid effects and may reflect withdrawal from catecholamine and serotonin receptors. Rajabizadeh et al (2009) reported psychosis as an atypical withdrawal symptom of tramadol subsiding a few days after suppression of withdrawal symptoms [86].

To survey and assess the drug dependence and abuse potential of tramadol in those without a history of substance abuse, subjects (N = 23 males) being treated for tramadol dependence but with no prior history of substance abuse were surveyed by interview and compared to a control group of addicts and healthy men. Physical dependence was assessed using the 10-item opiate withdrawal scale (OWS), and psychological dependence using the Addiction Research Centre Inventory-Chinese Version (ARCI-CV). It was concluded that long-term infrequent abuse using high doses of tramadol without a history of misuse of other substances had a clear risk of dependence [87]. This was different to the outcome experienced by those who used low-dose tramadol over an extended period where the risk of physical dependence and withdrawal symptoms were lower than prototypic opioid effects [88-91]. The development of physical dependence from tramadol therefore appears dose-related, and administration of 800 mg/day tramadol leads to similar levels of opioid

physical dependence as 60 mg/day morphine. It is possible that acute dosing regimens are not sufficient to produce pronounced opioid-like effects but that a sustained high dosing regimen of tramadol results in the development of neural adaptations characteristic of other mu-agonists [92].

Abuse Potential

A. **Animal Studies**

As mentioned previously discordance between animal and human studies should be borne in mind when considering treatment effects in animal experiments that may not be comparable to those for humans, in some species [93]: human data should therefore be given greater weight.

Animal studies have shown tramadol to be a weak reinforcer of self-administration compared to other pure opioid agonists like morphine and based on these observations, it has often been described as an atypical opioid analgesic with mild opioid-like effects[90]. Several drug discrimination studies using rats support the abuse potential of tramadol: tramadol displays symmetrical generalisation to morphine. A study using rats reported that a full generalisation was achieved with morphine at doses of 2.37 mg/kg or higher and with tramadol at doses of 32 mg/kg or higher. The generalisations by morphine and tramadol were blocked by the concomitant administration of naltrexone (0.01 - 0.05 mg/kg) [94].

B. **Human Studies**

Abuse liability studies among humans have generally reported that tramadol has less abuse liability than morphine. Although, when administered to recreational drug users [95] as well as nondependent individuals [88], tramadol was often recognised as an opioid and was reported as a “liked drug.” Tramadol did not significantly increase subjective ratings associated with reinforcement [88]. However, recent research identified a patient's preoperative narcotic (tramadol), benzodiazepine, and tobacco use correlated to the amount of postoperative narcotic prescriptions filled in the 3 months following surgery and concluded a predisposition to substance abuse may be a characteristic which leads to increased postoperative tramadol use [96]. In a randomized double-blind complete crossover study (N = 10) conducted at the National Drug Dependence Treatment Centre in New Delhi, tramadol (100 mg) was found to have greater abuse potential (even in therapeutic doses) than placebo but less than or comparable to buprenorphine [97].

It has been generally accepted that parentally administered tramadol is less likely to be identified as an opioid because M1 production is minimalised since first-pass metabolism is avoided. Hence the abuse of tramadol is much reduced through intravenous administration when compared to ingestion.

Reports on tramadol abuse include case reports and case series on tramadol abuse from India [36]: This case series underscores the need for caution, while using tramadol in substance-dependent patients. In a series of seven cases, all men, tramadol use had begun with a prescription of tramadol for opioid detoxification, for headache and body pains, and

as an alternative to injectable opioids. All subjects reported euphoria with tramadol use. They subsequently sought treatment at a drug treatment centre following difficulties with the drug: doses of tramadol ranged from 50 to 1500 mg per day, often being significantly above doses recommended for therapeutic use [36]. The action of tramadol on the monoaminergic system gives antidepressant-like properties that some feel, protects against abuse, but a case study reported that this property was sought after to improve mood, as if it were a stimulant, highlighting the risk of inducing abuse despite this feature of the drug [98].

More recently, functional magnetic resonance imaging (fMRI) was used to study the effects of tramadol on the reward system in humans to assess drug abuse or dependence. Tramadol significantly reduced anxiety ($Z = -2.513$, $p = 0.012$) and enhanced vigour ($Z = -2.725$, $p = 0.006$) compared with placebo. By Mood Rating Scale, tramadol provoked contented ($Z = -2.316$, $p = 0.021$), relaxed ($Z = -2.236$, $p = 0.025$), and amicable feelings ($Z = -2.015$, $p = 0.044$) as well as increased alertness ($Z = -1.972$, $p = 0.049$) and contentedness domains ($Z = -2.174$, $p = 0.030$) compared with placebo. Several brain regions including nucleus accumbens (NAc) were activated during gain anticipation in the MID task under both tramadol and placebo. It was concluded that tramadol enhances the reward system and has the potential to precipitate drug abuse and/or dependence in humans [99].

Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Tramadol, like other opioids, is commonly used for acute and chronic pain conditions. The scientific evidence is extensive although mixed in terms of the efficacy of the drug as an analgesic. Multiple systematic reviews [100] suggest a role of tramadol in relief of various pain conditions including osteoarthritis, neuropathic pain, refractory restless leg syndrome [101], chronic low backache, cancer pain. The analgesic effects of tramadol are known to be significantly less than that of hydrocodone/acetaminophen (schedule C-III, USA) but like that of pentazocine (schedule C-IV, USA) or, superior or like the propoxyphene/acetaminophen combination (schedule C-IV, USA) in relieving postoperative pain [23].

New once-daily (OD) formulations of tramadol have been marketed in various countries, to offer the advantage of a reduced dosing regimen and to help improve patients' compliance. Three RCTs demonstrated similar rates of efficacy between OD tramadol and immediate-release (IR) or sustained-release (SR) formulations. An open trial on long term tolerability showed that OD tramadol is generally safe in rheumatological pain treatment [102]. A 5-day randomised, open-label, comparative, parallel group, multi-centre trial conducted at three centres in India (N = 204) found a fixed-dose combination of tramadol-diclofenac showed a significantly greater reduction in pain intensity compared with tramadol-paracetamol, resulting in better analgesia in patients suffering from moderate to severe pain due to acute musculoskeletal conditions, post-operative pain following orthopaedic surgery, or acute flare of osteoarthritis and rheumatoid arthritis [103].

However, a recent Cochrane systematic review by Wiffen [104], that looked at the use of tramadol for chronic pain related. Ten studies (12 reports) of randomised controlled trials (with placebo or active controls, or both) with 958 adult participants (aged 24-87 years) were included. All the studies enrolled participants with chronic malignant tumour-related pain who were experiencing pain intensities described as moderate to severe, with most experiencing at least 4/10 with current treatment. Tramadol doses ranged from 50 mg as single dose to 600 mg per day; doses of 300 mg per day to 400 mg per day were most common. The results were judged to be very low quality because of widespread lack of blinding of outcome assessment, inadequately described sequence generation, allocation concealment, and small numbers of participants and events. It was concluded that there was limited and low-quality evidence that tramadol medication was or was not as effective as morphine for pain relief [104].

A review of Cochrane studies assessed 9 reviews (152 studies and 13,524 participants) and found very low quality evidence for the use of opioids including tramadol for treating cancer pain. It was concluded that although most will receive some pain relief from opioids, 1-2 out of 10 will experience intolerable adverse effects [105]. Similarly, other evidence from randomised controlled trials (RTCs) found that tramadol produced pain relief in some adults with pain due to cancer but there was no evidence at all for its effectiveness in children and adolescents [106].

In addition, a further Cochrane review (2017) of 6 randomised, double-blind studies where tramadol was used to treat neuropathic pain in adults (aged 50 to 67 years, N = 438, doses 100 to 400 mg/day) for four or six weeks was published. The research found the evidence in favour of tramadol for pain relief to be limited and of low-quality (different types of neuropathic pain, bias, small sample size and, limited duration study). That is, the evidence of benefit from tramadol was of low or very low quality: bias was felt to have increased the apparent benefits of tramadol in the treatment of neuropathic pain [107]. Tramadol has also been suggested in combination with paracetamol to treat fibromyalgia, but there is limited evidence to support or refute this combination pharmacotherapy [108].

A study carried out by tramadol manufacturer Grunenthal suggests tramadol to be effective in the treatment of arthrosic and neuropathic pain, with a value of Number Needed to Treat (NNT) of 3.4, and in mixed nociceptive-neuropathic pain, especially in persistent or chronic pain. An additional therapeutic benefit noted is that tramadol maintains a good tolerability profile in elderly subjects with reduced pharmacological interactions and a low incidence of constipation [109].

The availability of tramadol as a non-controlled drug has made it attractive as an analgesic despite growing evidence of less than optimal effectiveness. The Change Pain Latin America (CPLA) advisory panel of experts in the management of chronic pain (August 2016), listed the main reasons for tramadol's high significance as a wide spectrum non-oncological pain treatment option as, broad efficacy; inconspicuous safety profile; fewer opioid-like side effects than classical opioids; and lower abuse risk. The CPLA felt that more stringent regulations would have a significant impact on the availability of tramadol, especially for

outpatients and lead, at least in Latin America, to regression to older and frequently inadequate pain management methods [110].

Tramadol has been considered as a preferred therapeutic option over other opioids within psychiatric populations due to its lower abuse potential. The evidence however is not robust. For instance, the effectiveness of tramadol in patients with depression related to chronic pain has been questioned [108]; case reports have highlighted the risk of serotonergic syndrome when tramadol and sertraline are combined [111-113]; the combination of tramadol with selective serotonin reuptake inhibitors (SSRIs) for managing symptoms of refractory depression [114], has not been widely applied and finally; although the Canadian Psychiatric Association (CPA) have proposed tramadol as a third-line treatment for obsessive-compulsive disorder (OCD) [115], this has recently been challenged based on the poor quality of evidence [116].

Tramadol has also been proposed for the management of opioid use disorders. It has been used for the management of detoxification as well as slower reduction programmes (extending over a few weeks to a few months) from outpatient settings [36]. Tramadol has been reported to be used for dependence on all opioids including natural opioids such as poppy husk, raw opium [afeem], heroin, dextropropoxyphene, pentazocine. In India, tramadol is used for the treatment and management of opioid use disorders [37].

Tramadol has also been used as a standalone treatment for premature ejaculation (PE) [117]. However, in a systematic review and meta-analysis of the usefulness of tramadol to treat PE, between-trial heterogeneity and variable reporting quality of the available evidence were noted. The variability across placebo-controlled trials in terms of the tramadol dose evaluated and the treatment duration does not permit any assessment of a safe and effective minimum daily dose. The long-term effects and side effects, including addiction potential, for men with PE have not been evaluated in the current evidence base [118].

Listing on the WHO Model List of Essential Medicines

Tramadol is not listed on the WHO Model List of Essential Medicines.

Tramadol was considered for inclusion in the EML/EMLc in 2017. The EML Expert Committee considered that the evidence presented in the application shows tramadol to be a suboptimal treatment for cancer pain compared with morphine and other opioids. The Expert Committee therefore did not recommend the addition of tramadol as a treatment for cancer pain to the EML or EMLc.

Tramadol is listed in several national essential medicines lists including: Algeria [2007], Bhutan [2012], Botswana [2012], several provinces of China, Congo [2013], Cook Islands [2007], Côte d'Ivoire, Croatia [2010], Dominican Republic [2005], Ecuador [2009], Egypt [2006], Ethiopia [2015], Ghana [2010], Honduras [2009-11], India [2011], Iraq [2010], Jamaica [2008], Jordan [2011], Maldives [2011], Montenegro [2011], Morocco [2008],

Myanmar, Namibia [2008], Peru [2010], Philippines [2008], Republic of Moldova [2009], Rwanda [2010], Serbia [2008], Seychelles [2010], Slovakia [2010], Slovenia [2010], South Africa [2006], Sri Lanka [2009], Sudan [2010], Tajikistan [2009], Thailand [2012], The former Yugoslav Republic of Macedonia [2010], Timor-Leste [2004], Togo [2012], Trinidad and Tobago [2010], Tunisia [2008], Ukraine [2010], United Republic of Tanzania [2013], Vietnam [2008], Uruguay [2011]).

In a study to investigate the presence of tramadol on national essential medicines lists (NEMLs), 112 documents published between 2002 and 2014 were evaluated. The NEMLs included 24/34 (71%) developing or emerging countries classified as low income by The World Bank, 40/50 (80%) countries classified as lower-middle income, 37/55 (67%) countries classified as higher-middle income, and 8/38 (21%) developing or emerging countries and territories classified as high income. Thirty-nine (39) countries were in Africa, 23 in the Americas, 30 in Asia (including the Middle East), 8 in Europe, and 12 in Oceania. Of these, tramadol was included in about half as the only second-line analgesic agent [122].

Marketing Authorisation (as a Medicinal Product)

Marketing authorisations for tramadol as a medicine are held by many companies internationally. For instance, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) granted Bristol Laboratories Ltd a Marketing Authorisation (MA licence) for Tramadol 50mg capsules (PL 17907/0110) as a prescription only medicine [POM] used to treat moderate to severe pain. Approved MAs containing tramadol hydrochloride in Europe are listed on the internet (https://www. Pharmacompass .com/eu-ctd-dossier-marketing-authorisation/tramadol-hydrochloride/). Table 3 lists manufacturers of tramadol hydrochloride and the host country.

Table 3 Global Manufacturers of Tramadol Hydrochloride with Active Pharma Ingredients (API) licences (LePro PharmaCompass OPC Ltd, 2018, https://www.pharmacompass.com/listed-active-pharmaceutical-ingredients/tramadol-hydrochloride).

Company Name	Country	Company Name	Country
Biotechnica Pharma Global	Algeria	Remedy Labs	India
Delta Finochem P Ltd	India	Rusan Pharma Ltd.	India
Dipharma Francis S.r.l.	Italy	Supriya Lifescience Ltd	India
Globe Quimica Ltd	Brazil	Saneca Pharmaceuticals	Slovakia
GVK Biosciences	India	Shandong Xinhua Pharmaceutical Co Ltd	China

Jubilant Life Sciences Ltd	India	Titan Laboratories Pvt Ltd.	India
Hoventa Pharma	India	Virupaksha Organics Ltd	India
Nishchem International Pvt. Ltd	India	Viruj Pharma	India
Pellets Pharma Limited	India	Wavelength Pharma	Israel
Qualitek pharma	India	Zim Laboratories	India
Raks Pharma Pvt. Ltd.	India		

Industrial Use

Industrial use of tramadol is not reported

Non-Medical Use, Abuse and Dependence

Tramadol HCl, marketed as ULTRAM in the USA, was introduced as a non-scheduled drug in April 1995 based on the assumption that the risk of abuse was low and did not warrant a scheduled status. However, approval was contingent upon the development of a surveillance programme, to be overseen by an independent steering committee, which would detect unexpectedly high levels of abuse. The surveillance programme included the systematic collection and scientific evaluation of reports of suspected abuse in high-risk populations and all spontaneous reports of abuse received through the FDA MedWatch system. Most of the abuse cases (97%) at the time were found to occur among individuals with a history of substance abuse and the abuse was confined to isolated pockets with significant populations of street drug abusers. The data was used to support the decision not to schedule tramadol in the 1990s [123].

The risk-management programme in the United States has been modified over the past decade to accommodate Ultracet (ULTRAM and acetaminophen) in 2001 and generic tramadol in 2002 and provided an opportunity to study the potential changes in abuse as the generic and combination products became available [123]. Survey data continued to suggest in the early 2000s that the diversion of Ultram and other tramadol products was low, and overall, diversion investigators did not consider tramadol to be a problem in their respective jurisdictions [124].

Historical epidemiological reports and surveillance studies indicated that tramadol diversion, abuse and overdose increased between 2003 and 2009 in the United States [125, 126], leading several states (Kentucky, Arkansas, Wyoming and Tennessee) to change the scheduling of tramadol to a more stringent category (Schedule IV): tramadol was scheduled nationally in 2014 [23, 71]. Recent clinical research suggests that the abuse liability of tramadol may have been previously underestimated with respect to oral administration, as

the earlier preclinical and clinical studies employed parenteral dosing. As production of the metabolite M1, is largely dependent on hepatic metabolism, concentrations of M1 are much higher after oral, relative to parenteral administration [45, 127].

There is almost 15 years of post-marketing epidemiologic abuse related data in the scientific literature and from the adverse events reporting system (AERS) since tramadol's commercial availability in the U.S. The case reports demonstrate an addiction liability of tramadol: drug craving, dosage escalation, self-harming to be prescribed more tramadol, continued consumption despite adverse effects, and visiting multiple physicians to obtain more prescriptions for tramadol [123, 124]. The increasing evidence includes epidemiologic abuse-related data in the published scientific literature, as well as data from national and state data systems that track drug abuse. Case reports describe abuse is for its euphorigenic and sedating effects. According to the updated NSDUH data analyzed by DEA, the estimated number of individuals who have used tramadol products non-medically at least once in their lifetime increased from 1,990,000 in 2008 to 2,614,000 in 2011. For each year from 2002 to 2011, the number of individuals reporting lifetime nonmedical use of tramadol resulting from the NSDUH survey was lower than the corresponding numbers for hydrocodone or oxycodone [23].

The prevalence of prescription medicines among opioid users in China was explored and tramadol was found to be the most commonly used prescription opioid (27.3%). It was demonstrated that abuse of prescription medicine was widespread among opioid users in China [128]. Whereas following an initial Iraqi Community Epidemiology Working Group set up by the Iraqi Ministry of Health, with support from the US government to explore the nature and extent of drug and alcohol use in Iraq, tramadol was identified as a new drug in the Iraqi drug scene [129].

Epidemiological studies in the past have reported a lower tendency for tramadol misuse when compared to other opioids [124] and therefore assumptions were made that its use would be less likely to be associated with diversion. However, newer information indicates a growing number of tramadol abusers in some Middle East and African countries, where diversion is a predominant source of the drug.

Specific country reports

Arab Republic of Egypt

The National Council for Drug Control and Treatment conducted a study 'The National Comprehensive Survey of the Phenomenon of Substance Abuse in Egypt', in 2017, which was subsequently presented as a report to the WHO by the Head of the National Council for Drug Control & Treatment, Egypt [130]. Results from a national survey found that the abuse of tramadol was still a national concern despite scheduling of the drug. This has been attributed to illegal trafficking and inexpensive pricing. In the 2012/1013 survey 7.6% of the sample abused drugs: of these 31.5% reported misuse of tramadol. There was also the issue

with the availability of tablets containing higher than recommended doses 150 mg and 200 mg instead of 50 mg and 100 mg leading to problematic use and dependence [130].

In a study to explore tramadol misuse liability among Egyptian university students, it was found that prevalence of use was 12.3%, with higher prevalence in male (20.2%) compared to female students (2.4%). There has been a large increase in the number of people seeking help with tramadol use from 38.7% of the addict population in 2011 to 71.1% in 2016: the number of addicts overall has risen from 8589 to 33, 030. Age at onset of tramadol use was 17.6 ± 2.1 years with one-fifth using tramadol as their first drug: using tramadol alone was unusual [131]. Egypt put tramadol under strict national control because of widescale abuse of the analgesic, but, in 2015, nearly 70% of those treated in a state-run addiction facility were still addicted to the painkiller. The national authorities in Egypt believe that the control of tramadol should be extended beyond national control measures because of the negative impact of the abuse of the drug [132].

Cameroon

The presence of tramadol in the roots of Sarcocephalus latifolius trees in Northern Cameroon was recently attributed to point contamination with tramadol. It was initially believed to be a plant derived source of the drug, but the origin was traced to tramadol tablets bought locally in downtown Maroua. The soil in the surrounding area was found to be highly contaminated with tramadol when analysed by accelerator mass spectrometry [133]. Recent reports have highlighted the widespread misuse of tramadol in farming communities and the practice of feeding tramadol to cattle, to prolong ploughing. The drug inevitably had found its way into the soil such is the extent of its use in the region [134]. International control was advocated.

Ghana

Tramadol is on the list of essential medicines in Ghana, the dosage approved being 50 mg raising to 100 mg in hospitals. The limit for daily dosing is 400 mg in line with international standards. Tramadol is imported from 10 different countries both as a prepared product and as a powdered form, that is pressed into tablets locally. Capsules and injectable solutions are also imported. Some parts of Ghana there are no pharmacies or health centres or medical prescribing doctors so that those in pain resort to other means such as itinerant traders. The problems reported with the abuse of tramadol that have intensified since 2017. Unregistered high-dose tramadol 120 mg, 225 mg, 250 mg, 450 mg and 500 mg have been uncovered.

Intelligence gathered across the country pointed to routine abuse of tramadol by youth, students, market women and commercial drivers of unbranded 'falsified' pharmaceutical products. These are sold from village stalls, over-the-counter in shops or from unregistered chemists and by itinerant hawkers. Tramadol being usually mixed with energy enhancers, alcoholic beverages and possibly cannabis (https://www.myjoyonline.com/lifestyle/2018/march-28th/fda-seeks-inter-agency-collaboration-to-end-tramadol-abuse.php). Even though some governments have put deterrents in place against the trafficking of tramadol, manufacturers and importers find ways to deliver their shipments.

However, in the national debate over the future of scheduling, the Ghanaian Medical Association and Pharmaceutical Society of Ghana are opposed for fear that patients will be negatively affected, while the Food and Drug Administration (FDA) are in favour because of concerns about misuse and its impact on society [132].

Finland

In Finland, the prevalence and predictors of non-medical substance use, and the association between non-medical substance use and fatal poisoning or history of drug abuse was investigated. In half of the studied cases, at least one drug was detected without a prescription. Clonazepam, alprazolam and tramadol were the most prevalent non-medical findings in these cases (6.6, 6.1 and 5.6%, respectively). In Finland, the risk of non-medical use of prescription drugs was especially high in cases with a history of drug abuse (88.5%) and in fatal poisonings (71.0%) [135]. Fatal poisoning was reported as a risk when tramadol was consumed with other drugs or alcohol [78].

Latin America

Tramadol plays an important role in the treatment of pain in countries with low to non-existent access to controlled opioid analgesics. Data show a steady increase of tramadol from about 15 million patient treatment days in 2010 to 35 million in 2015 in Latin America [136]. There are concerns that the scheduling of tramadol would impact upon the use of this drug for pain relief.

North-eastern Nigeria

The emergence of tramadol among drug users in the northeast region of Nigeria within the last decade has represented a major landmark in drug use events in the sub-region. A retrospective cross-sectional study was conducted using clinical records of 237 drug users attending the addiction clinic of Federal Neuropsychiatric Hospital, Maiduguri, North-eastern Nigeria. The prevalence of tramadol abuse was high within the cohort, with over half (54.4 %, N = 129). The majority (78%, 95% CI = 54.1 - 65.7) met the ICD-10 diagnostic criteria for tramadol dependence. Classically, 93% were males and 87% [67.4%, 95% C.I. = 59.9 - 73.4] were in the 18 to 37 years age range. Of importance was that almost all (91%) of the subjects obtained the drug without prescription from drug vendors and 12.4% were first introduced to tramadol by healthcare professionals. To address tiredness (28.7%) or to prolong sexual intercourse (22.5%) were the reasons given for continued use. It was thought that a lack of adequate control by the relevant regulatory agencies had contributed to the misuse of tramadol [137].

Northern Iran

Tramadol is a widely prescribed drug in Iran and reports of its abuse have been growing for more than a decade. In a study is to evaluate tramadol-related deaths in Tehran (between

2005 and 2008), autopsy samples were evaluated. Of 20,000 cases tramadol was detected on 294 occasions alone or together with other drugs: most of the cases were young male adults. Tramadol-related deaths in 2008 were 32.5 times more frequent than in 2005 [138]. In a study to investigate tramadol sale by Iranian pharmacies it was found that over half of patients (92/162, 56%) who had sought tramadol from a pharmacy, did not have a prescription. Nearly two-thirds (64%) met criteria for dependence (i.e., the need to continue to take the drug for feelings of psychological wellbeing, unable to cease taking the drug despite advice or signs of physical damage etc). Most, as in other studies (89%) were < 30 years old and 55% < 18 years old. The high prevalence of people under 18 years of age seeking tramadol was thought to be a more widespread trend [139].

More recent research seems to support the assertion of adolescent use of the drug. In a study to estimate the point prevalence of tramadol misuse in a sample of Iranian adolescents a prospective survey examined smoking status, substance misuse (alcohol, cannabis and ecstasy) and related factors in Ilam city, Iran. Grade 10 male and female students (n=2000) were recruited using multistage sampling. The prevalence of lifetime misuse of tramadol was 4.8% (7.6% males; 1.8% females). Tramadol misusers were twice as likely to report substance use during the past month (2.2, CI 1.1-4.4). Longitudinal studies to investigate the possible role of tramadol as a gateway drug in the development of substance abuse was advocated [140].

Tramadol poisoning has also been reported to be a common cause of acute pharmaceutical poisoning in Iran. Seizure was the most common symptom among tramadol-intoxicated referrals to a poison centre in Tehran. The mean ingested dose was 1971.2 mg. Blood gas on admission indicated acute respiratory acidosis (pH 7.3 ± 0.1, PCO_2 49.7 ± 8.6 mmHg and HCO_3^- 24.1 ± 3.8 mEq/L). There were significant differences between tramadol-intoxicated cases with and without a seizure about the time interval between ingestion and admission to hospital: the time interval being significantly longer in seizure group [141]. It was concluded in 2017 that tramadol poisoning has turned into a major cause of admission to Iranian emergency departments, especially among young males who have a history of mental disorders and substance abuse [142] and was a particular worry in College students [143].

Norway

A national cohort of tramadol users was investigated in Norway. The study population of 154 042 adult Norwegians (who redeemed ≥ one tramadol prescription in 2012) was stratified into four groups according to opioid use 2 years before the first tramadol prescription in 2012 and were followed-up until 2016. Six percent of opioid naïve tramadol users (no opioid use 2 years before tramadol use in 2012) became recurrent users (received opioids annually during the 4-year follow-up), almost doubling their mean opioid consumption (66 to 108 defined daily doses [DDD]). One-quarter proceeded to strong opioids or were co-medicated with benzodiazepines, one-third with Z-hypnotics. Among former weak opioid users, 39.8% became recurrent users and 18.7% proceeded to strong opioids: mean opioid consumption increased slightly. Among former strong opioid and users in palliative care, 61%, 70% became recurrent users and developed a similar prescription

pattern (high and increasing mean opioid consumption). Many patients who developed recurrent opioid use received prescriptions which substantially conflicted with existing dosing guidelines [144].

Poland

In a study to explore opioid use in Poland it was found that most users (two thirds of subjects) lived in cities whose population was higher than 100 inhabitants (63.7%) and the majority were male (76.9%). Codeine and tramadol were most frequently used on their own. Tolerance and dependence were observed: drugs were not always taken by the oral route and the pharmacological activity of the drugs used were sometimes modified with other substances [145].

Yemen

In a study to investigate the misuse of prescription and over-the-counter (OTC) drugs in community pharmacies in Aden city, Yemen, qualitative in-depth-interviews (N =15) were undertaken with suspected drug misusers recruited through community pharmacies. Most interviewees were male (*n* = 11/1 5) with an age range of 21¯40 years. Benzodiazepines, tramadol and ketoprofen were the most commonly abused drugs reported. The study highlighted the practice of mixing different OTC and prescription drugs with Khat to heighten the effects or manage pain and drug misuse by females and by health care professionals. The study also suggested that physicians and pharmacists feared counselling those seeking these drugs, because of the risk of violence [146].

Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

There is growing evidence that the adverse effects of tramadol are consistent with the adverse effects associated with other opioids. Abuse, dependence and overdose of opioids have become serious public health problems in the United States [147]. Total outpatient prescription opioid purchases for adults totalled 152.8 million prescriptions with Hydrocodone, Oxycodone, and Tramadol accounting for about 80 % of these (61.7, 33.0, and 26.5 million prescriptions, respectively) in 2015. The economic cost to the individual, highlights the extent to which tramadol has pervaded American society: Tramadol, had the highest average out-of-pocket expenses ($513) for all outpatient prescriptions per person including for hydrocodone and oxycodone ($400, $495) and was nearly twice that of codeine ($262) [148].

Drug-driving

As a further indication of the impact of tramadol on public health problems tramadol has been recognised as a substance that is not compatible with driving. For instance:

- The National Safety Council's Alcohol, Drugs and Impairment Division's changed tramadol and its metabolites to Tier I (mandatory) from Tier II (optional) due to changes in prevalence and concerns about their potential for causing impairment whilst driving [32, 149]
- Non-prescribed use of tramadol and benzodiazepines (classed as psychoactive prescription drugs) were common in subjects suspected of drug-impaired driving in Sweden during 2006-2009. As has been found in other jurisdictions the Swedish drug-drive population were young, not-in-treatment, multi-substance users. In total, 2225 subjects were identified using the Swedish Forensic Toxicology Database. The median age (range) was 34 (15-80) years and the vast majority of subjects were male (1864, 83.8%). Non-prescribed use was found in over half of cases (1513, 58.7%). For tramadol there were 192 cases (40.3%) [150].
- In Denmark, as part of the EU 6th framework DRUID programme (Driving Under the Influence of Drugs, Alcohol and Medicines) blood samples were screened for 30 illegal and legal psychoactive substances and metabolites as well as ethanol. Danish legal limits were used to evaluate the frequency of drivers violating the Danish legislation while limit of quantification (LOQ) was used for monitoring positive drivers. Tramadol was not included in the Danish legislation therefore the general cut off, as decided in the DRUID project was used. Young men (median age 31 years) were over-represented among injured drivers who violated Danish law for alcohol and drugs. Tramadol (3.2%) was the second most frequently detected medicinal drug at concentrations above the laboratory limit of quantitation (LOQ), behind diazepam (4.4%). Poly-drug use was observed in 112 (13%) seriously injured drivers. Tramadol was detected above DRUID cut-offs in 2.1% of seriously injured drivers. This is 3.5 times that observed in a Danish survey of randomly selected drivers [151].

Licit production, consumption and International Trade

In March 1995, the Food and Drug Administration (FDA) approved tramadol as a non-controlled, non-traditional, centrally acting analgesic under the trade name ULTRAM® (50 mg tramadol) for marketing in The United States. Since then a myriad of other tramadol formulations have been approved for marketing as immediate-release, extended release and sustained products. Generic products are also freely available.

Illicit Manufacture and Traffic and related Information

The National Forensic Laboratory Information System (NFLIS) is a Drug Enforcement Administration (DEA) database that collects scientifically verified data on analysed samples in the United States at state level and from local forensic laboratories. It also includes data from the 'System to Retrieve Information from Drug Evidence' (STRIDE), which includes data

on analysed samples from DEA laboratories. The data show that for each of the years from 2000 through 2012, tramadol was present in drug exhibits seized during law enforcement activity. The tramadol exhibits seized by law enforcement involving drug abuse indicate significant diversion of tramadol in the United States. Tramadol exhibits increased from a total of 82 in 2000 to 1,806 in 2012 (NFLIS data). In 2010, this number was greater than the number of exhibits shown to contain pentazocine (96, Schedule IV), but less than the number of hydrocodone (45,627, Schedule III), codeine (3,679, Schedules II, III, V), and buprenorphine (10,167, Schedule III) exhibits [71].

Abuse of tramadol has been reported to be a serious problem in Egypt during 2011 and 2012. Information available to the International Narcotics Control Board (INCB) suggest that tramadol was smuggled into Egypt from China and India.

Data provided by UNODC (July 2017) on global tramadol traffic showed a steady increase in seizures between 2007 and 2015. Evidence indicated that all drug seizures were associated with Benin, but the pattern in seizures varied on a year-by year basis. In the WHO annual review of psychoactive substances questionnaire report for the 39th ECDD meeting (2017), it was reported that the combined number of seizures from 8 countries had gone up from 3403 (2014) to 6022 (2016).

Current International Controls

Refer to Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Current and Past National Controls

Refer to Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Other medicinal and Scientific Matters Relevant for a recommendation on the Scheduling of the Substance

At the end of 2017 UNODC warned of the increase in trafficking and consumption of tramadol. In the last 5 years seizures of the drug have risen from 300 kg to more than 3 tonnes. Benin, Nigeria, Ghana, Togo, Niger, Sierra Leone, Cameroon and Cote d'Ivoire were highlighted as the major transit or destination countries. The imported tablets are then trafficked by criminal organisations to areas of the Sahel where armed groups and terrorist organisations such as Boko Haram in Nigeria and the Islamic State of Iraq and the Levant in Libya, have partial control. According to UNODC tramadol trafficking plays a direct role in destabilising the region (World Report, May 2018) [134].

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