

Assessment of tramadol

1. Substance Identification

- A. International Nonproprietary Name (INN): tramadol
- B. Chemical Abstract Service (CAS) Registry Number:
27203-92-5 (base)
36282-47-0 (hydrochloride salt)
- C. Other Names:
2-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexanol
- D. Trade Names: Acugesic, Adamon, Adolonta, Amanda, Ammitram, Amadol, Anadol, Analab, Analgan, Anamol, Biodalgic, Biodol, By-madiol, Calmol, Captanil, Ceparidin, Cloritram, Contramal, Contradal, Controdol, Crismal, Crismol, Crispin, Cronus, Dalgión, Dholopax, Doctramado, Dolan, Dolana, Doldonos, Dolipran, Dolnam, Dolol, Dolomat, Dolotram, Dolotramine, Dolzam, Domadol, Dorcen, Dorless, Dormatrix, Dromadol, Dubeban, Dubepan, Ecodolor, Eufindol, Exopen, Famadol, Fastfen, Gemadol, Greatamol, Imadol, Ixprim, J.V.Dol, Lucidol, Lumidol, Mabron, Maditer, Madol, Malgic, Mandolgin, Mardol, Matradol, Maxitram, Milidol, Minidol, Monocrioxo, Nardor, Nobligan, Nodsenal, Nomal, Nycodol, Omnidol, Opan, Pacmadol, Paindol, Pantec, Pendol, Pengesic, Pharmadol, Piralgin, Plasadol, Pinnadol, Poltram, Predalgic, Profundol, Prontofofort, Protradon, Ramadol, Rofty, Rofy, Roladol, Romadol, Sefmal, Seminac, Sensitan, Simatral, Sintral, Sonamol, Starmadol, Supridol, Sylador, Syndiol, Takadol, Taladol, Tamadal, Tamadol, Tamolan, Taxiflan, Telurin, Temdol, Termed, Terpan, Theradol, Tilamadol, Timarol, Tinasen, Tioner, Tiparol, Topalgic, Trabar, Trabarin, Trabilin, Tradol, Tradolan, Tradolgesic, Tradolint, Tradonal, Tragesic, Tralic, Tralgidol, Tralgiol, Tralgit, Trama, Tramabene, Tramac, Tramacap, Tramacet, Tramache, Tramada, Tramaden, Tramadex, Tramadil, Tramadin, Tramadol, Tramadolar, Tramadoleos, Tramadolios, Tramadolor, Tramadomeol, Tramadon, Tramafran, Tramagelic, Tramagetic, Tramagit, Tramahexal, Tramake, Tramal, Tramalan, Tramalgin, Tramaline, Tramamed, Tramaphar, Tramavics, Tramax., Tramazac, Tramed, Tramedo, Tramium, Tramoda, Tramomet, Tramquel, Tramundal, Tramundin, Tranal, Trandol, Transidol, Trapelene, Trapidol, Trasedal, Tratadol, Traumet, Travex, Traxel, Treadyl, Tremadol, Trexol, Triadol, Trodon, Trol, Troma, Trosic, Trumen, Ultracet, Ultradol, Ultram, Ultramex, Updol, Urgendol, Vestradol, Volcidol, Winpain, Wintradol, Xmadol, Xolodam, Xymel, Zaldiar, Zamadol, Zamudol, Zodol, Zumalgic, Zydol, Zytram
- E. Identification Characteristics:

Tramadol hydrochloride salt is a white crystalline powder. It has a melting point of 179-181°C and is readily soluble in water and ethanol and has a pKa of 9.41. The analytical profile of tramadol has been described. Data pertaining to GC-MS [1], GC-NPD [2], HPLC-DAD [3, 95] and LC-MS [4] have been described.
- F. WHO Review History: Tramadol was pre-reviewed first at the 28th meeting in 1992, which did not recommend critical review on the basis of its low abuse liability as indicated by human studies on its subjective effects and the absence of significant abuse. When tramadol was pre-reviewed again at the 32nd meeting in 2000, the Committee noted significant numbers of cases of withdrawal syndrome and dependence reported as adverse drug reactions, as well as its potential to produce dependence of the morphine type, and recommended critical review of tramadol. In its 33rd meeting the Committee decided that

the information was not sufficient to recommend international control of tramadol, but was adequate to recommend that WHO keep the drug under surveillance. For this reason the substance is under review again on the agenda of its 34th meeting.

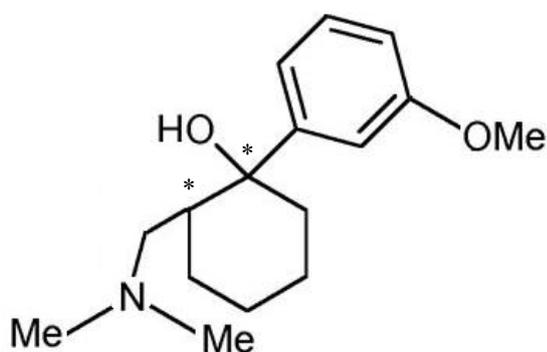
2. Chemistry

A. Chemical Name (\pm) -*cis*-2-[(dimethylamino)methyl]-1-(*m*-methoxyphenyl)cyclohexanol

IUPAC Name: Tramadol

CA Index Name: Tramadol

B. Chemical Structure:



Molecular Formula: C₁₆H₂₅NO₂

Molecular Weight: 263.4

C. Stereoisomers: 4 enantiomers:

(+/-)-*cis*-2-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexanol
 (+/-)-*trans*-2-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexanol

(Note: tramadol is commercially available as the racemate of the *cis* form)

3. General pharmacology

Described in this section are studies that have examined the pharmacological actions of tramadol. Tramadol is a synthetic, centrally acting opioid analgesic with a potent active opioid metabolite. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: weak binding of parent and higher binding of M1 metabolite to μ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. The M1 metabolite elicits strong μ -opioid effects. It produces less respiratory depression than other opioids and has no significant cardiac effects. It reduces the seizure and sweating thresholds. It reduces postoperative shivering.

Neuropharmacology

Tramadol is a synthetic opioid analogue of codeine first synthesised in 1962 by Grunenthal in an attempt to reduce common opioid adverse effects such as respiratory depression [5].

In general, tramadol has been found to be an opioid agonist with selectivity for the μ receptor but with some weak affinity for the κ and δ receptors [6-7]. The affinity for the μ receptor is approximately 10-fold less than codeine and 6000-fold less than morphine [6-7]. This may partly be explained by the presence of a methylated phenolic moiety like codeine, compared to the (demethylated) phenolic moiety of morphine. Hence, opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite (ODT or M1) to μ -opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ -opioid binding. [8].

Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound. In one study, only 30% of its activity in humans was blocked by naloxone concluding that 70% of the activity is not related to the μ -opioid receptor [113].

The affinity of the M1 metabolite to the μ -opioid receptor is 20 to 40 times greater than that of codeine and 160 to 300 times greater than tramadol, while the affinity of morphine is 7 to 12 times greater [111].

Studies of the effects of tramadol on various neurotransmitter systems have shown that the racemate and the two enantiomers of tramadol hydrochloride have varying effects [7,9-10]. The (+)-tramadol enantiomer is a selective agonist of μ -opioid receptors and inhibits serotonin (5-HT) reuptake. Whereas (-)-tramadol mainly inhibits noradrenaline (NA) reuptake, stimulating α_2 -adrenergic receptors but has little affinity for μ -opioid receptors [5]. The (+)-enantiomer was found to have 10-fold higher analgesic activity than the (-)-enantiomer. Ultimately, the synergistic effect of these enantiomers produces the analgesic activity of the racemate. In addition to the direct analgesic effect at the opioid receptor, the monoaminergic activity (in particular α_2 -adrenergic stimulation) has a significant analgesic contribution by blocking nociceptive impulses at the spinal level [5,7].

The recent Grunenthal study (Grunenthal Department of Biochemical Pharmacology, Germany, Gillen et al 2000) was conducted to characterize tramadol and its metabolites M1, M2, M3, M4 and M5 at the cloned human μ -opioid receptor and concluded that the metabolite (+)-M1 is responsible for the μ -opioid-derived analgesic effect. The metabolite (+)-M1 showed the highest affinity ($K_i=3.4$ nM) to the human μ -opioid receptor, followed by (\pm)-M5 ($K_i=100$ nM), (-)-M1 ($K_i=240$ nM) and (\pm)-tramadol ($K_i=2.4$:M). Agonistic activity followed the following rank order of intrinsic efficacy: (+)-M1 > (\pm)-M5 > (-)-M1. The metabolites (\pm)-M2, (\pm)-M3 and (\pm)-M4 displayed weak affinity ($K_i>10$:M) [112].

Analgesic effects

The analgesic effect of tramadol is thought to be due to the synergistic activity of the racemate with further contribution from the M1 metabolite. Studies of 98 patients recovering from gynaecological surgery receiving initial intravenous (i.v.) 50-200 mg doses (followed by patient controlled analgesia) found that the (+)-enantiomer produced comparable analgesia to the racemate but both therapies provided greater analgesia than the (-)-enantiomer [11]. It was also found that the (+)-enantiomer produced higher incidences of nausea compared to the racemate and in addition to efficacy criteria testing (where the responder rates were similar for the (+)-enantiomer and racemate) it was concluded that the racemate was the preferred analgesic therapy.

Studies of the affinity, potency and efficacy of (+/-)-tramadol and its metabolites (M1, M2, M3, M4 and M5) at the cloned human μ -opioid receptor showed that the (+)-M1 metabolite had the strongest binding affinity and agonistic activity at the receptor. It was therefore suggested that the (+)-M1 metabolite was responsible for the μ -opioid derived analgesic effect [12]. In addition, although *ex vivo* studies in mice indicated opioid binding of the M1 and M5 metabolites, only the M1 metabolite exhibited analgesic activity *in vivo* based on tail-flick response tests [7].

The use of tramadol as a centrally acting analgesic compound compared to other opioid and non-opioid compounds has been studied in various clinical situations. This is reviewed in the Clinical Studies section, but in general, tramadol has been found to be equally effective as pethidine (meperidine), morphine and pentazocine in relieving moderate pain. However, morphine was found to be superior in relieving severe pain [13]. In double-blind controlled studies, 100 mg oral tramadol produced analgesic effects greater than a placebo with peak analgesia occurring 1 to 4 hours post dose [8]. In another study, the minimum effective serum concentration for effective analgesia was found to be 20.2-986.3 $\mu\text{g/L}$ (median 287.7 $\mu\text{g/L}$) for racemic tramadol and 0.9-190.5 $\mu\text{g/L}$ (median 36.2 $\mu\text{g/L}$) for the M1 metabolite. This was determined in 40 postoperative patients receiving an intravenous loading dose (50-200mg) followed by patient controlled analgesia (maximum dose 500mg/4 hours) [14].

Respiratory effects

The potential for respiratory depression is commonly associated with opioid analgesics and occurs due to a decrease in the sensitivity of the respiratory centre to carbon dioxide. This results in a decreased tidal volume and respiratory rate [8]. Researchers have compared the respiratory effects of tramadol with other opioid analgesics. Houmes et al evaluated the effects of intravenous tramadol hydrochloride (50 mg) and morphine sulphate (5 mg) on patients' oxygen saturation. 6 out of the 50 patients assessed exhibited a decreased oxygen saturation (<86%) following morphine administration; however this did not occur in any patient administered tramadol [15]. Additional studies of 30 adult patients by Vickers et al reported a decreased respiratory rate for tramadol (2 mg/kg i.v.) which was significantly less than morphine sulphate (0.143 mg/kg i.v.) [16]. During the study it was also observed that morphine affected both the end-tidal alveolar carbon dioxide (CO_2) pressure and tidal volume. Tarkkila et al compared the effects of tramadol and oxycodone [17]. Administration of 0.6 mg/kg i.v. tramadol or 0.04 mg/kg i.v. oxycodone to 36 spontaneously breathing patients showed little difference between tramadol and the placebo for the end-tidal CO_2 concentration, inspiratory-expiratory difference, minute volume and respiratory rate. However, oxycodone appeared to produce significant respiratory depression [17]. In a randomised, double-blind, placebo-controlled study of 88 children (2-10 years) receiving i.v. tramadol (1-2 mg/kg) or pethidine (1 mg/kg), tramadol produced significantly less respiratory depression than pethidine [18]. This was also observed by Schaffer et al during a study of 60 children receiving postoperative 0.75-1.5 mg/kg intramuscular (i.m.) tramadol or 0.15-0.2 mg/kg nalbuphine [19]. Tramadol appeared to affect the respiratory rate less than nalbuphine.

It should be noted, however, that following excessive dosage such as in overdose situations, tramadol may produce life-threatening respiratory depression [5,7].

Overall, it has been reported that tramadol produces less respiratory depression than other opioid

analgesics such as morphine, pethidine and nalbuphine.¹ Study results (measurements of decreased tidal volumes and respiratory rates) vary with the dose of drugs administered. In addition, tramadol's peak effect is dependent upon formation of the M1 metabolite and is likely to occur at a later time than that of morphine, the active comparator.

Central nervous system (CNS) effects

Tramadol has been noted to have produced some CNS effects, notably; dizziness, sedation, headache (generally 16-33% of patients) and to a lesser extent euphoria, CNS stimulation (e.g. tremor, agitation, anxiety, hallucinations), dysphoria and seizures (between 1-14%) [20-21]. In particular, less than 1% of patients suffered seizures, and was found to be linked to predisposition such as epilepsy, alcohol/drug withdrawal or antidepressant therapy. Conversely, studies in mice found tramadol had some anticonvulsant effect which appeared to be κ -receptor mediated as it was unaffected by the μ -antagonist, naloxone [22].

Gastrointestinal effects

Patients taking tramadol have reported some gastrointestinal effects. These include nausea, vomiting and constipation (9-40%) with a limited number (<5%) reporting a change in appetite [20]. In obstetric patients, tramadol produced more emetic effects (nausea) than morphine or pethidine [23]. This is particularly observed following rapid i.v. administration in addition to vomiting and sweating. However, the potential for constipation appears to be significantly less for tramadol than for equipotent doses of codeine and paracetamol/aspirin [24].

Antidepressant effects

Predictive studies in mice using the forced swim test have evaluated the potential antidepressant effects of tramadol [63]. This is based on the reported effects of tramadol on monoamine reuptake. Using (+/-) tramadol, (+)tramadol and (-)tramadol, it was shown that both (+/-)tramadol and (-)tramadol produced a dose-dependent reduction in immobility; the (+)tramadol enantiomer had no significant effect. It was also found that inhibition of noradrenaline synthesis blocked the effect of the racemate. This was not observed using the serotonergic blocker methysergide nor the opioid antagonist naloxone. It was concluded that tramadol racemate and its (-) enantiomer had some antidepressant-like effect in mice, probably mediated by the noradrenergic system [63].

Clinical studies on use for acute pain

Tramadol was first used in therapeutic analgesia in Germany in 1977. Since this time its use has become more widespread and it has been registered/marketed in most countries by 2005.

Tramadol has been clinically evaluated in all surgical disciplines, including general, orthopaedic, paediatric and cardiothoracic surgery [5]. There have been many reviews of the clinical use of tramadol for pain management [5,7,13].

In general, tramadol has been described as a centrally-acting opioid analgesic with potency/efficacy similar to that of pethidine but has compared favourably to various analgesic agents in acute situations [5] but not necessarily emergency medicine [96]. Studies have shown it to be more effective than non-steroidal anti-inflammatory drugs (NSAIDs), pentazocine and multiple dose dextropropoxyphene-paracetamol

¹ There seems to be some controversy among regulatory authorities on the question to what extent the respiratory depression is less than with other opioids. However, most countries seem to warn for the respiratory depressant properties in the product documentation. In the USA, for instance the official leaflet says: "1. Respiratory Depression: Tramadol should be administered cautiously in patients at risk for respiratory depression. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose." Also France, Ireland and Japan have more or less similar warnings. However, in the Netherlands the official leaflet says: "Contrary to morphine, tramadol has no respiratory depressant properties in an analgesic dosage over a large range." and in Switzerland the leaflet contains a similar statement.

preparations. In addition, tramadol and paracetamol were found to reduce the severity of pain and photophobia associated with moderate-to-severe migraine headache [97]. Intra-operative studies showed tramadol did not antagonise the hypnotic effects of volatile inhalational agents (such as isoflurane and nitrous oxide) and was not associated with significant lightening of anaesthesia or any cardiorespiratory side-effects or accidental awareness [5,67-68]. Tramadol has shown greatest effectiveness following typically parenteral administration in post-operative situations for moderate to severe surgical pain. In particular, tramadol has been used for post thoracotomy pain (single i.v. bolus dose), abdominal surgery (i.v. infusion), groin incision day-case surgery, acute dento-alveolar surgical pain (oral), day-case laparoscopic sterilisation (i.v. infusion), orthopaedic surgery (i.v. patient-controlled analgesia, oral and i.m.), paediatric surgery (patients over 12 months old, i.m., i.v. and oral droplet form), obstetrics (i.m. during labour and epidural administration post-caesarean section surgery – although the latter is not necessarily recommended), acute ureteric colic (subcutaneous), acute trauma and myocardial ischaemic pain (i.v.) [5,7,13]. During these applications, tramadol was found to have minimal respiratory depression (unless used in combination with other CNS depressants), a relatively slow onset time (at 3 mg/kg i.v.), significantly less pain in recovery from day-case surgery (1.5 mg/kg i.v.) and provided significant efficacy in treating intra- and post-operative shivering. Nausea and vomiting was observed with suppository tramadol [69] and when used in combination with paracetamol for acute migraine pain [97].

Use for chronic pain

The therapeutic use of tramadol has also been evaluated in the treatment of both cancer related and non-cancer related chronic pain [5,7,13].

Tramadol has been used in the treatment of pain due to chronic pancreatitis, osteoarthritis, neuropathy, systemic scleroderma and chronic lower back pain. Rauck et al studied 390 elderly patients suffering from chronic pain conditions receiving tramadol (50 mg oral dose) and codeine-paracetamol (30-300 mg) as necessary. On average the daily dose was 244 mg for tramadol and 140.7-1407 mg for codeine-paracetamol. 55% of patients of each group rated analgesia as good to excellent; however, a significant number of patients discontinued tramadol intake due to adverse effects [70]. In 264 patients with osteoarthritis, tramadol (300 mg/day oral) was compared with propoxyphene (300 mg/day oral) it was found that there appeared to be improved analgesia and reduced sleep disturbance in the tramadol group [71]. Furthermore, tramadol could be beneficial as an adjunct to NSAID (e.g. naproxen) osteoarthritic therapy [72]. In patients suffering from chronic lower back pain, twice daily 100 mg oral sustained release tramadol preparations appeared to reduce side effects and was of comparable efficacy compared to multiple (four times daily) 50 mg oral doses [73-74]. During studies of oral tramadol for chronic cancer related pain, it was found to provide good to excellent analgesia and had comparable tolerability but fewer side-effects than morphine or buprenorphine [75-77].

Other effects

During a study by Tarkkila et al involving i.v. tramadol and oxycodone, there appeared to be no significant cardiac effects (i.e. heart rate or systolic arterial pressure) [17]. However, Schaffer et al found i.m. tramadol and nalbuphine decreased heart rate and diastolic pressure but with no effect on systolic blood pressure [19]. Furthermore, Vickers et al found tramadol produced a statistically significant (but not clinically significant) increase in systolic and diastolic blood pressure compared to pethidine in 30 postoperative adults receiving patient controlled analgesia [16].

Observations by De Witte et al regarding thermoregulative effects found that overall tramadol had similar effects to other opioids (reducing the vasoconstriction and shivering threshold) but it also reduced the sweating threshold [25]. Specifically it has been noted that tramadol reduces postoperative shivering [7]. There may also be some urinary retention but this occurs less commonly than potent opioids [5].

4. Toxicology, including adverse reactions in humans

Animal and human studies indicate that tramadol toxicity is dose-dependent and can result in coma, random clonic movements, decrease in body temperature, hypotonia, hallucinations, nausea, vomiting, bradycardia, convulsions, respiratory depression and apnoea. Other CNS depressant or monoamine antidepressant compounds may exacerbate any toxic effects. In humans, there have been some reported non-fatal instances of tramadol intoxication and related deaths, worldwide.

Toxicity in Animals

A study of the anticonvulsant and proconvulsant effects of tramadol, its enantiomers and M1 metabolite in rats compared kindled and non-kindled rats. Racemic tramadol and both enantiomers (+) and (-)-tramadol induced anticonvulsant effects in kindled rats at analgesic dosage [27]. However, at slightly higher doses of racemic tramadol (30 mg/kg), seizures were observed in kindled but not non-kindled rats. Moreover, (-)-tramadol induced myoclonic seizures at 30 mg/kg in most kindled rats but not in non-kindled rats; however seizures were observed in some non-kindled rats at 10 or 20 mg/kg. Seizures were also observed following (+)-tramadol and M1; higher doses caused significant respiratory depression, however. Overall, it was concluded that kindling enhances the susceptibility of rats to seizures following tramadol (and its enantiomers) administration. Thus, a pre-existing lower seizure threshold increases the risk of tramadol-induced seizures.

The LD₅₀ in mice and rats has been determined to be 350 mg/kg and 228 mg/kg, respectively, following an oral dose. In addition, an LD₅₀ of 200 mg/kg and 286 mg/kg has been reported in mice and rats, respectively, following a subcutaneous dose [28]. In subacute and chronic toxicity studies, toxic symptoms such as convulsions, behavioural disorders were observed at doses beginning at 25 mg/kg [29].

In rhesus monkeys, Yanagita observed only slight pupil dilation in monkeys receiving 4 mg/kg subcutaneous tramadol [30]. Those receiving 8 mg/kg exhibited decreased awareness, diminished spontaneous motility, licking and mydriasis; those receiving 16 mg/kg manifested uneasiness and later nausea and vomiting which later subsided and the animal became inattentive to environmental stimuli. Finally, monkeys receiving 32 mg/kg developed grand mal convulsions about 30 minutes post dose.

Tramadol has not been found to be mutagenic in the Ames Salmonella microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters [31]. There appeared to be some mutagenic effect in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. In addition, no effects on fertility were observed at oral doses up to 50 mg/kg in male rats and 75 mg/kg in female rats. However, tramadol has been shown to be embryotoxic and foetotoxic in mice, rats and rabbits at maternally toxic doses 3-15 fold higher than the maximum human dose or higher (120 mg/kg in mice, >25 mg/kg in rats and >75 mg/kg in rabbits). Toxicity manifested as decreased foetal weights, skeletal ossification and increased supernumerary ribs. In one rabbit study a 300 mg/kg maternal dose was lethal to the embryo and foetus. However, it was not teratogenic at these maternally toxic doses and there appeared to be no harm to the foetus at doses that were not maternally toxic. Furthermore, no tramadol-related teratogenic effects were reported in the progeny of mice, rats and rabbits (up to 140 mg/kg in mice, 80 mg/kg in rats and 300 mg/kg in rabbits via various routes). Although maternal toxicity was observed at all doses, toxic effects were only evident in progeny at higher doses where maternal toxicity was more severe.

Overall, these studies indicated that tramadol did not pose a genotoxic risk to humans.

Toxicity in Humans

The frequency of adverse reactions have been reported in 7198 patients receiving tramadol in Phase IV clinical trials and in 550 patients with chronic non-malignant pain [20-21]. Some of these adverse effects have been presented in Section 3 – General Pharmacology.

Specifically, in the 7198 patients receiving tramadol during Phase IV clinical trials, adverse events were noted in 16.8% of patients. The most common effects were dizziness, CNS effects, nausea, autonomic system disorders, dry mouth and sedation. The more frequent adverse effects appeared to be dependent upon on the dose and route of administration. More effects were noted with 200 mg dosage compared to 50 mg or 100 mg, and with intravenous injection compared to oral or intramuscular administration [21].

In addition, in the 550 patients receiving “Ultram” in a double-blind study (375 patients over 64), the most frequently reported events were related to the central nervous system and gastrointestinal system [20]. Some of these may have been due to underlying disease or concomitant medication, however, and the overall frequency of adverse effects were comparable to the codeine, aspirin and paracetamol control groups. Nonetheless, adverse effects primarily included dizziness, nausea, constipation, headache and somnolence (between 25-46% up to 90 days following start of therapy). Other less frequent effects included vomiting, sweating, dyspepsia, dry mouth and diarrhoea (between 10-17% up to 90 days). All these effects had also been reported at 7 and 30 days post therapy with similar proportional frequency. Some rarely experienced adverse effects (frequency less than 5%) were also recorded including; weight loss, euphoria, amnesia, cognitive disturbance, skin rash, hypotension and tachycardia. Anaphylactoid reactions have also been observed in some patients and often occurred following the first dose; patients with a history of anaphylactoid reactions to codeine and other opioids may be at higher risk if such reactions with tramadol, estimated incidence 1 in 700,000 patients [20].

Typical symptoms of tramadol overdose as observed in patients presenting at poisons centres included; mild tachycardia, hypertension, nausea, lethargy, convulsions, coma and respiratory depression/arrest [32]. No serious cardiotoxicity was reported and naloxone reversed sedation and apnoea in 50% of the patients. Due to the high affinity of the M1 metabolite for the μ -receptor, it has been hypothesised that the presence of this metabolite has a significant contribution to the analgesic and toxic effects of tramadol. However, although naloxone can usually reverse tramadol-induced respiratory depression and coma, other toxic symptoms thought to be due to inhibition of monoamine reuptake cannot be reversed by naloxone [5, 13]. Overdose resulting in mild serotonin syndrome can cause agitation, confusion, tachycardia and hypertension.

As tramadol is an opioid, its effects may be exacerbated by other opiates/opioids (e.g. morphine, codeine, oxycodone, methadone and heroin) and compounds that can cause sedation and respiratory depression (e.g. benzodiazepines, alcohol, barbiturates and GHB). However, much of the toxicity of tramadol appears to be due to the monoamine reuptake inhibition rather than the opioid effects [32]. Hence, concomitant use of monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) should be avoided [5,98]. Serotonin syndrome may occur if the SSRIs, sertraline, fluoxetine, citalopram and paroxetine are ingested [33-34,99]. Venlafaxine, a serotonin and noradrenaline reuptake inhibitor (SNRI) may also produce synergistic toxic symptoms [35]. An increase in CNS catecholamines may result in convulsions in susceptible patients [36]. The rate of convulsions with tramadol has been reported to be 1 in 7000 by the Committee on Safety of Medicines in the U.K. (mainly with large i.v. doses) [5]. Further contraindications based on the metabolism of tramadol include concomitant administration of quinidine (a selective inhibitor of CYP2D6) and propafenone which result in elevated serum concentrations of tramadol and reduced concentrations of M1 metabolite [37-38]. Administration with warfarin resulted in an increase in the INR and may in part have been due to CYP2D6 polymorphisms [100]. However, the clinical relevance of this has not been determined [7,20]. During postmarketing surveillance, there were also some rare reported cases of digoxin toxicity [20].

Cases of Tramadol Intoxication in Humans:

Non-fatal Cases

There have been some reported cases of tramadol intoxication, particularly in Europe (e.g. Germany, United Kingdom and Switzerland) and the United States but there are no global estimates of the number of cases [32,34,39-44]. Of the various international agencies and drug centres contacted (e.g. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and National Reintox centres) there was no

information available regarding tramadol exposure. Tramadol does not feature in the top ten drugs mentioned to the London (UNK) National Poisons Information Service (NPIS) by medical staff treating suspected poisonings [45]. However, tramadol constituted 1714 United States emergency department mentions in a Drug Abuse Warning Network (DAWN) report for 1995-2002 and although numbers increased initially, they were unchanged from 2000-2002 [101]. Furthermore, 127 suspected cases were reported by 7 poison centres in the United States between October 1995 and August 1996 [32]. These cases involved lethargy, nausea, agitation, tachycardia, seizures, coma, hypertension and respiratory depression. It is not known how many of these were confirmed cases. Urine drug analysis in 19 of these patients did not detect opiates, however, the technique used may not have been applicable to tramadol. 4 cases involving inappropriate tramadol administration to infants have also been reported [42-44,102]. In the cases reported by Riedel and Bianchetti, the infants suffered respiratory depression and coma, but responded to naloxone and diazepam treatment. In one of the cases involving a 6 month old, serum tramadol concentrations were determined to be 2.1 mg/L and 0.7 mg/L after 15 hours and 20 hours, respectively [42]. Tobias reported seizures following an inadvertent 4 mg/kg dose of tramadol [43] as did Kronstrand [102]. Sachdeva and Jolly have reported a tramadol overdose resulting in coma, respiratory depression and tachycardia that required prolonged opioid-antagonism (naloxone) treatment [41]. Goeringer et al reported 4 cases of drug-impaired drivers where tramadol was detected but other drugs (in particular opioids) were also detected [39]. However, the exact symptoms of intoxication (if any) were not stated.

Overall, there is a paucity of confirmed reported cases of non-fatal intoxication, particularly with supporting analytical evidence. Analytically, tramadol is a chemically basic compound and thus should be detected using routine chromatographic analysis. It may not be detected, however, using immunoassay techniques that may be used during emergency drugs of abuse screening.

Fatal Cases

As for non-fatal cases, there are no global estimates of the number of deaths related to tramadol. Except for a mention from DAWN (report 2000) for Minneapolis, Minnesota, there was no specific mention in any other state. There have been at least 28 published fatalities involving tramadol from the United States and Europe (e.g. Germany, Poland, France and Switzerland) [47-51,103-105] and 23 unpublished fatalities (from the United Kingdom and Luxembourg) [52-54]. A selection of these cases is shown in Table 1. However, with the majority of instances involving multiple drugs the exact toxicological significance of tramadol is unclear in some cases. Goeringer et al reported a total of 12 cases involving tramadol but it was detected at concentrations that exceeded typical therapeutic values (up to 0.4 mg/L) in only 4 of these [39]. However, the authors detailed the potential synergistic effects with the other drugs detected (e.g. opioids and monoamine uptake inhibitors). Of the 22 unpublished cases taken from investigations within the United Kingdom (1998-2005), the vast majority involved suspected suicidal overdose [52-53]. Other drugs were invariably involved (particularly tricyclic and SSRI antidepressants) but the tramadol concentrations determined in the post mortem blood (typically greater than 6 mg/L) were generally much greater than therapeutic concentrations. In one unique case report involving only tramadol, acute liver failure was cited as the mode of death [106], however, the patient received concomitantly prednisolon, azathioprin and naproxen and therefore other drugs with a known hepatotoxic potential provide an alternative explanation in this case (communication to WHO by Grünenthal Chemie).

The WHO Uppsala Monitoring Centre (UMC) reported over a 2 year period of world wide PMS-data 253 cases of death (1.0 %) and 12 cases of sudden death (0.05 %), out of 22753 reported adverse effects (unpublished, communication to WHO, 2005). These reports need to be seen to the background of a huge patient exposure. For 2003 and 2004 alone the exposure was approximately 1.55 billion patient treatment days worldwide.² (Based on IMS dat, provided in communication to WHO by Grünenthal Chemie).

² The methodology of collecting and interpreting pharmacovigilance data will be discussed under 7.2 on the agenda.

Case No.	Patient Details	Reference	Drugs detected	Concentration(s)	Comments
1	49 yr M	Lusthof et al [47]	Tramadol + 7-aminoflunitrazepam	Blood tramadol = 13 mg/L	Suspected overdose.
2		Ripple et al [35]	Tramadol + venlafaxine + promethazine + paracetamol	Blood tramadol = 0. mg/L	Suffered back pain. Undergoing alcohol detoxification. Prescribed SSRIs. Suffered seizures.
3	U F	Moore et al [48]	Tramadol	Blood tramadol = 20 mg/L	Tramadol overdose.
4	U M	Musshoff et al [49]	Tramadol	Blood tramadol = 9.6 mg/L	Only tramadol.
5	30 yr F	Michaud et al [50]	Tramadol + alprazolam + alcohol	Blood tramadol = 38.3 mg/L	History of depression.
6	41 yr M	Hernandez et al [51]	Moclobemide + clomipramine + tramadol + diazepam + caffeine	Blood tramadol = 10.89 mg/L	History of depression, apparent mixed overdose. Fatal serotonin syndrome reported.
7	28 yr F	Goeringer et al [39]	Tramadol + dextromethorphan + propoxyphene + morphine	Blood tramadol = 0.05 mg/L Blood ODT = 0.46 mg/L	History of drug abuse. Multiple drug overdose. Possible effect of ODT and other CYP2D6 substrates.
8	57 yr F		Doxepin + tramadol	Blood tramadol = 0.48 mg/L Blood ODT = 0.02 mg/L	Acute doxepin overdose but possible synergistic effect of tramadol.
9	36 yr M		Propoxyphene + alprazolam + tramadol	Blood tramadol = 0.16 mg/L Blood ODT = 1.84 mg/L	Back pain. Acute combination drug intoxication. Opioid and other CYP2D6 substrates present.
10	39 yr M		Tramadol + amitriptyline + diazepam	Blood tramadol = 1.43 mg/L Blood ODT = 0.03 mg/L	Positional asphyxiation. Additional acute drug intoxication.
11			Tramadol + amitriptyline + hydrocodone	Blood tramadol = 2.47 mg/L Blood ODT = 0.06 mg/L	Acute tramadol intoxication. Possible interaction with amitriptyline and hydrocodone.
12	32 yr M		Tramadol + propranolol + trazodone + desipramine + alcohol	Blood tramadol = 22.59 mg/L Blood ODT = 0.34 mg/L	Multiple drug overdose.
13	44 yr M		Tramadol + carisoprolol + meprobate + nordiazepam + alcohol	Blood tramadol = 1.13 mg/L Blood ODT = 0.46 mg/L	Suicidal decapitation in train incident.
14	75 yr M	Elliott [52]	Tramadol + morphine + amitriptyline	Blood tramadol = 26 mg/L Blood ODT = 2.9 mg/L	Rheumatoid arthritis. Suspected overdose.
15	46 yr M		Tramadol + amitriptyline	Blood tramadol = 6 mg/L Blood ODT = 0.9 mg/L	Osteoarthritis, depression.
16	47 yr F		Tramadol + amitriptyline + diazepam + alcohol	Blood tramadol = 8.6 mg/L Blood ODT = 1.0 mg/L	Multiple sclerosis. Suicidal overdose.
17	80 yr M		Tramadol + alcohol	Blood tramadol = 6.3 mg/L Blood ODT = 0.45 mg/L	Osteoarthritis and Parkinson's. Suspected overdose.

Table 1. 17 reported fatalities involving tramadol.

5. Pharmacokinetics

Tramadol is rapidly absorbed following oral administration. It is metabolised in the liver by CYP3A and particularly CYP2D6-controlled pathways involving O-desmethylation, N-desmethylation and subsequent conjugation or sulphation. In healthy adults following oral administration (100 mg) the C_{max} is approximately 308 µg/L. The plasma half-life of tramadol is approximately 6 hours.

Tramadol is rapidly absorbed following a single 100 mg dose (mean absolute bioavailability 68%) with the bioavailability increasing (to 90-100%) following multiple 100 mg dose administration. This is thought to be due to a saturate first-pass hepatic metabolism [7-8,55]. Concomitant food intake also appeared to increase absolute bioavailability but was not thought to be clinically relevant [55]. Bioavailability has also been found to increase with age and following intramuscular administration reaches 100% [8]. The volume of distribution following oral dosage has been reported to be 2.7 L/kg with plasma protein binding of 20% [7,20].

Tramadol undergoes extensive first-pass metabolism following oral administration. The kidneys excrete approximately 90% of an oral dose and 10% in the bile. Furthermore, approximately 10-30% is found as unchanged drug in the urine with 60% excreted as metabolites [20]. Tramadol is metabolised in the liver via two main metabolic pathways involving CYP3A and CYP2D6 isoenzymes to form active O-desmethyl metabolite (M1 or ODT) or inactive N-desmethyl metabolite (phase I reactions) [5,7]. The M1 metabolite may undergo further conjugation or sulphation (phase II reactions). The particular phase I route is largely determined by the liver concentration of Cytochrome P450 CYP2D6 sparteine-oxygenase. A high concentration favours O-desmethylation, where as a low concentration yields the N-desmethyl metabolite (nortramadol) [56]. Studies using poor sparteine metabolisers (as a CYP2D6 activity marker) showed significantly higher metabolic ratios of tramadol O-desmethylation (4.4) than extensive metabolisers (0.8) [57]. In humans, 5 phase I reaction products have been detected and 6 phase II products [5,58-60].

The metabolites have been identified as:

- M1 = O-desmethyltramadol (ODT)
- M2 = N-desmethyltramadol (nortramadol)
- M3 = N-didesmethyltramadol
- M4 = tri-N,O-desmethyltramadol
- M5 = N,O-didesmethyltramadol
- M1-conjugates (glucuronides and sulphates)
- M4-conjugates (glucuronides and sulphates)
- M5-conjugates (glucuronides and sulphates)

The major metabolites are M1, M1-conjugates, M2, M5 and M5-conjugates. The M3, M4 and M4-conjugates are formed in only minor quantities.

Parameter	Single Oral 100 mg dose		Multiple Oral 100 mg dose		i.v. 50 mg	i.m. 50 mg
	Tramadol	M1 metab.	Tramadol	M1 metab.	Tramadol	Tramadol
C_{max} (µg/L)	308	55	592	110	347.4	193
t_{max} (h)	1.6	2.97	2.25	2.43	NA	0.75
AUC (µg/Lh)	2649	722	3679	835	1556	1582
$t_{1/2\beta}$	5.64	6.69	6.71	6.98	5.5	5.5

- C_{max} = maximum plasma concentration
- t_{max} = time to reach C_{max}
- AUC = area under the plasma concentration-time curve from zero to infinity
- $t_{1/2\beta}$ = terminal elimination half life
- NA = not available/reported

Table 2. Pharmacokinetic data for tramadol and its M1 metabolite following oral, i.v. and i.m. dosage. (table taken from Scott and Perry [7])

Table 2 shows pharmacokinetic data following oral, intravenous and intramuscular administration of tramadol hydrochloride in healthy adults [7,55].

Mean peak plasma concentrations of 280-308 µg/L have been reported approximately 2 hours following single 100 mg tramadol dosage [7,55]. In addition, peak serum concentrations of 613 µg/L and 409 µg/L have been observed 15 minutes and 2 hours, respectively in healthy adults, following 100 mg i.v. tramadol [13,62]. In patients with renal and/or hepatic impairment, the elimination half-life and tramadol half-life are increased [8]. The plasma half-life of tramadol and the M1 metabolite is approximately 6 hours and 9 hours, respectively [13].

Tramadol pharmacokinetics can be influenced by other drugs, particularly those that effect the enzymes involved in tramadol metabolism. As previously mentioned, concurrent administration of quinidine (a selective inhibitor of CYP2D6) and propafenone can result in elevated serum concentrations of tramadol and reduced concentrations of M1 metabolite [37-38]. Conversely, concomitant use of carbamazepine, which is a known inducer of hepatic enzymes, results in a 50% reduction in the terminal elimination half-life of tramadol [8]. As a result of chronic high dose carbamazepine therapy a two-fold increase in the dose of tramadol maybe required [20].

6. Dependence and abuse potential

Tramadol has been used therapeutically as an analgesic compound in both acute and chronic pain situations. It has an analgesic effect in moderate pain comparable to pethidine and morphine but has fewer adverse effects. It is primarily used in the treatment of postoperative moderate to severe pain. Abuse of tramadol appears to be associated with the prevalence of opioid abuse. Some preclinical animal studies indicated that tramadol may have a low abuse potential, however, clinical studies and post-marketing surveillance programmes have found that there is the possibility of dependence and abuse particularly in patients with a previous history of opioid dependence/abuse.

A. Studies in animals

As tramadol was found to be a weak µ-agonist, the possibility of tolerance and dependence has been evaluated in different animal species.

Miranda and Pinardi compared the antinociceptive activity (tolerance) and physical dependence (using naloxone) of tramadol and morphine in mice. It was found that unlike morphine, tramadol is unlikely to induce tolerance and physical dependence [64]. Other animal studies reported that tramadol did not precipitate or suppress physical withdrawal symptoms in morphine-dependent rats, mice and rhesus monkeys [30,39,65-66]. Yanagita further showed that in rhesus monkeys tramadol did produce mild withdrawal symptoms in non-dependent subjects but it was concluded that compared to other published data, tramadol had a lower physical dependence potential than pentazocine and codeine [30]. It was also found that the reinforcing effect of tramadol was considerably less than that of pentazocine or codeine and a certain degree of tolerance may be developed to tramadol.

B. Human studies

The purpose of a study by Preston et al. was to assess the abuse potential of tramadol. Tramadol (75, 150 and 300 mg), morphine (15 and 30 mg) and placebo were tested intramuscularly in 12 male patients who although had a history of narcotic abuse, did not show any signs of drug withdrawal. Subjective, behavioral and miotic changes were assessed prior to dosing and intermittently for 12 h after drug administration. Morphine produced typical subjective effects, opiate identifications (*Feel the Drug*, *High*, and *Like the Drug* scales of the Subjects Drug Rating Questionnaire) and miosis. Tramadol 75 and 150 mg were not different from placebo. Although tramadol 300 mg was identified as an opiate (*Feel the Drug* VAS), it produced no other morphine-like effects significantly (*High* or *Like the Drug* scales) [37].

Additional studies by Cami et al reported no antagonistic/agonistic effects of (i.m.) tramadol in 6 opioid-dependent patients (undergoing methadone maintenance) [78]. The subjective, behavioural and physiological effects were comparable to the placebo. It was concluded that although tramadol appeared to have a low abuse liability, higher doses should be studied further.

A recent published study by Zacny profiled the subjective, psychomotor and physiological effects of tramadol in recreational drug users [110]. It was found that in a placebo-controlled randomised, crossover, double-blind study, compared to the other drugs tested (morphine and lorazepam) 100 mg of tramadol induced miosis and increased the “feel drug effect”, drug-liking ratings, “flushing, dizzy, lightheaded” and “take again” ratings. Tramadol did not appear to impair psychomotor performance. Morphine (mu-opioid, 1st active positive control) also did not impair psychomotor performance, but lorazepam (the CNS depressant benzodiazepine, 2nd active positive control) did impair psychomotor performance. [110].

Despite such studies indicating a low abuse potential for tramadol (even in high risk/high access populations such as healthcare professionals [107]), there have been a number of international reports of dependence and withdrawal (particularly in opiate-dependent individuals). In addition to anecdotal reports, incidences have also appeared in the literature [79]. In 1996 the U.S. FDA received 115 voluntary reports of drug abuse, dependence, withdrawal and intentional overdose associated with tramadol [80]. In 1998-9, the abuse potential was estimated to be 1 in 100,000 in the U.S. [5,81]. Importantly, further monitoring by the postmarketing surveillance Independent Steering Committee (ISC) between 1994-2004 found the rates of abuse of tramadol remained unchanged even with the introduction of new branded and generic products [108]. During the postmarketing surveillance program in the United States, 97% of abuse cases involved individuals with a history of substance abuse [81]. Furthermore, Liu et al found that tramadol produced a high abuse potential among opiate addicts as determined in 219 subjects where physical dependence, psychic dependence and craving scores were assessed [82]. In one case of tramadol dependence, the patient required methadone detoxification [83]. In another case, the patient had no history of substance abuse [84]. In addition, acute abstinence syndrome (as evidenced by restlessness, insomnia, abdominal cramps, diarrhoea and cephalgia) was observed in a patient who had an abrupt cessation in intake following a one year therapeutic period [85]. 422 cases of withdrawal following abrupt cessation or dose reduction have been reported to the postmarketing surveillance Independent Steering Committee (ISC) between April 1995-March 2000 [109]. These constituted 33% of the total number of adverse events received (1248) and included both typical (e.g. abdominal cramps, anxiety, depression, insomnia, sweating) and in some cases, atypical (e.g. panic attacks, unusual CNS symptoms and sensory phenomena) withdrawal effects.³

In a recent open, randomized, three-armed study in chronic pain patients from the USA, Adams EH et al. studied tramadol abuse in comparison with a negative (NSAIDs) and positive control (hydrocodone). The primary objective of the study was to compare the rate of abuse of tramadol with that of the negative control, and with medications containing the positive control.

A total of 11,352 patients were enrolled and surveyed by telephone 9 times over a 12 month period; in total, 87,180 interviews were completed. The majority of subjects (97.4%) were taking tramadol “as prescribed” or “less than prescribed” and well within the recommended daily dose. At the subject level, the rate of abuse reported associated with tramadol was 0.7%, which was equivalent to that associated with NSAIDs (0.5%), and statistically significantly less than the rate associated with hydrocodone (1.2%) [114].

Use and abuse of tramadol (including subjective effects in man)

Therapeutically, tramadol is available in the form of a powder, tablet, suppository or liquid formulation; therefore, the route of administration can be oral, rectal, intramuscular or intravenous injection. As

³ Upon a remark by Grünenthal Chemie, a manufacturer of tramadol, on an earlier version of this report, it should be remarked that in conformity with the definitions given by the ECDD in its 28th meeting in 1992 *abuse/harmful use* is characterized by use despite harm and that *drug dependence* is characterized by loss of control. It is important to distinguish between physical dependence, tolerance or withdrawal effects (all physiological adaptations) and drug abuse/harmful use. Dependence has both physiological and psychological aspects. Withdrawal is a time-limited symptom that occurs at discontinuation of continuous exposure to medication. It can occur with medications with almost no abuse potential, e.g., anti-hypertensives, tri-cyclic antidepressants, and steroids.

tramadol abuse appears to involve use of the pharmaceutical product rather than any illicit preparation, abuse can involve any of these routes.

There have been various anecdotal reports of tramadol abuse on the Internet [86]. Obviously, the validity and accuracy of these reports can be questioned, however, the reported effects are comparable to those mentioned during clinical studies. Overall, “users” describe some opiate-like symptoms and euphoria with possible physical and psychological dependence. Abuse of tramadol for its subjective euphoric effect has also been described elsewhere [81,87] and appears to be the main reason for abuse. Extracts of these reports (originating from the United States, Ireland, Thailand and Lithuania) are detailed below [86]:

Report 1 (USA 2000) – “Ultram” oral dose. “I started taking 150 mg and found the effects to be that of hydrocodone and oxycodone plus has a speedy effect, so it’s like the sense of well being, mellow effects of an opiate, and just a little speedy, enough to where you like it”.

Report 2 (Ireland 2001) – oral dose. “...I decided to try it out clubbing. It’s a lot like coming down off E [Ecstasy]. You don’t get any ‘rushes’ or any kind of high. I found it too incapacitating and the next day I could not pass water for 6-7 hours”....“I drank 4 pints of lager and took 300 mg and basically lost control of my senses. I was disorientated and paranoid and vomited for most of the night.”

Report 3 (USA 2001) – “Ultram” oral dose. “I enjoy opiates a good deal, and found that tramadol provided an adequate high”.....“it’s not quite as nice as oxycodone, morphine and the other ‘real’ opioids but it comes very close”.....“when I took about 150 µg of LSD a few hours after I had taken some tramadol it pretty much diminished the effects of the acid”.....“I kept 500-1000 mg around when I was taking tramadol daily. I found that after say a week or so of daily use some definitive tolerance developed, and some withdrawal symptoms could occur if use was suddenly stopped.”.....“I never found stopping to be a problem at all, but I’ve read internet postings where individuals had a very difficult time with tramadol dependency.”

Report 4 (Thailand 2001) – “I was recently prescribed tramadol for severe headache. Whereas one had no effects, upping the dose soon brought on very pronounced opiate effects, I began to feel extremely relaxed and pleasant with around 300 mg, in a slightly different way to codeine, the experience was cleaner, without the nausea, gastric effects and scratching.....”.....“I have a regrettably high tolerance to opiates and...I found increasing tolerance and dependence did occur with time, and I ended up taking 700 mg a go.”

Report 5 (Lithuania 2000) – oral dose. “A lot of people in my country enjoy a new drug, easily available in pharmacy stores without any problems. Personally I don’t like it because it produces a kind of state which you can experience on opiates.”... “I think it is more mentally addictive than physically..”

Report 6 (USA 2001) – “Ultram” oral dose. “Ultram is great, it is a very pleasant drug, and almost feels like cocaine without the paranoia. It removed all anxiety, body aches and pains.”.....“As long as it is taken only on occasion it is great, and withdrawals are not as likely.”

Report 7 (USA 2001) – “Ultram” oral dose. “I have been taking “Ultram” every day for about 3 years now for arthritis pain. When I first took it I took 150 mg and its effects were a lot like codeine and it had a mild speedy effect also. After taking it for a few weeks the codeine euphoria effect becomes less noticeable. I have quit taking it entirely for a couple of weeks with no adverse effects.”

Report 8 (USA 2004) – “Ultram” oral dose. “I have been taking 100-500 mg a day for 6 months to relieve my chronic lower back pain. I have been addicted to morphine for a year in 2001.”....“Ultram does not seem to be physically addictive to me. I vary my dose to fit my pain and my mood by the day”. ... “this is a wonderful drug, very few side effects and many benefits. No constipation...and a long duration of action relative to hydro or oxycodone.”

The US ISC also performed internet searches [81]. These searches indicated that within 2 months of tramadol’s launch 1995 in the US, there was extensive discussion of tramadol in the Internet, primarily by

individuals inquiring whether tramadol had mood-altering effects. While a very small number (< 12) indicated that tramadol could be used to alter mood or enhance effects of other drugs, over 90% of the discussions indicated that tramadol was devoid of any beneficial euphorogenic effect. Further reviews of internet drug abuse sites as early as in 1999 indicate little interest in tramadol. Evidently tramadol does not play an important role in the internet community as a drug of abuse despite continuously increasing exposure of the US and worldwide population to tramadol.

7. Epidemiology of use and abuse with an estimate of the abuse potential

At present, of the 72 countries which have responded to the questions on tramadol in the WHO Questionnaire, 69 countries indicated the medical use of tramadol. 64 As registered medicine and 5 in another way (exemptions, drug donations et cetera). In several countries combinations of paracetamol and tramadol are commercially available.

Of the countries that responded the question, 21 reported some abuse; 18 countries reported that there was no abuse and 33 had no information available. Ukraine reported widespread abuse of tramadol. Lithuania reported that the abuse was widespread among children and adolescents, until restrictions on sale were introduced in April 2005. In the other countries the abuse is relatively low. The United States of America reported a prevalence of 0.5% (lifetime use) among persons of 12 year and older.

Post-marketing surveillance data from USA In the USA, a comprehensive post-marketing surveillance program for "Ultram" was performed in conjunction with the FDA MedWatch system between April 1995 and June 1998 [81]. The data showed that from a peak of 2-3 cases per 100,000 patients (in mid-1996), the abuse rate and withdrawal frequency reduced significantly to 1 case per 100,000 patients in 1998. Furthermore, 97% of abuse cases involved individuals with a history of substance abuse (but not necessarily street drug abusers). The more recent data from the US FDA show large numbers of "drug abuse"/"drug dependence"/"withdrawal syndrome" reports (518/317/628) it received between March 1995 and 31 October 2001. Since the consumption data for the first two years of marketing (1995 and 1996) are missing, it is not possible to calculate the reporting rates for this period. A striking difference from the non-US data discussed in the preceding paragraph is the ratio of "drug abuse" and "drug dependence" reports to the reports of "withdrawal syndrome". In comparison with the non-USA data from the UMC database, there were many more abuse/dependence cases for every 100 reports of "withdrawal syndrome" in the USA. The IFPMA report [89] on post-marketing surveillance data collected by Grünenthal during the period from April 1994 to June 1998 also indicated the same tendency (283 cases of abuse/dependence and 171 reports of "alleged" abuse/dependence, as compared with 306 cases of withdrawal syndrome). The rate of reporting for tramadol abuse given in the IFPMA report was 2-3 cases "per month per 100,000 patients" initially, which went down to approximately one case per month per 100,000 patients later on. However, in the absence of comparable figures for other analgesics, it is difficult to compare tramadol with known opioid analgesics based on these data.

Substance Abuse Warning System (SAWS) SAWS data of Germany allow an early detection of the abuse of a newly emerging drug by drug abusers. No significant abuse of tramadol was known before 1990 [88]. The IFPMA report also analyses the SAWS data together with the sales data from Grünenthal for the period 1976 to 2000 [89]. While the number of reports on tramadol abuse increased after 1990, the rate of abuse per million DDDs showed a gradual decline from the peak value of 2.5 in the middle of the 1980s to one or less per million DDDs after 1995. Another IFPMA report [93] provides similar data for buprenorphine and pentazocine. Prior to their control in 1984 in Germany, the rates of abuse of these drugs were between 5 to 10 per million "Single Dosage Units". Since the "single dosage unit" was smaller than the DDD in the case of both pentazocine and buprenorphine (the high-dose buprenorphine preparations for substitution treatment were not sold in Germany during the 1980s), the data presented in the two IFPMA reports would signify that the rate of abuse of tramadol should have been significantly lower in comparison to buprenorphine and pentazocine in Germany during the early 1980s, when none of them was under national control.

Unfortunately an update of the source data is not possible as the system was terminated in the meantime.

Drug Abuse Warning Network (DAWN) data⁴ The DAWN data provided by the US government in response to the WHO Questionnaire 2002 are summarized earlier in this section. The percentage of ED mentions relative to number of prescriptions was 1.46% from 1997 through to June 2001 for tramadol, which was close to that of codeine (1.55%) and propoxyphene (1.86%). The IFPMA report [89] also discusses the DAWN ED data for tramadol in comparison with hydromorphone, hydrocodone, propoxyphene, chloridiazepoxide, amitriptyline and fluoxetine. The rates for 100,000 prescriptions were 16 for tramadol, 22 for propoxyphene and 26 for hydrocodone. Propoxyphene is the only drug compared with tramadol in both the government and the IFPMA reports. The two reports used different units for the comparison. In the government report, the difference in reporting rates between tramadol and propoxyphene was 1 to 1.27 whereas it was 1 to 1.37 in the IFPMA report. Although the precise origin of the small difference (about 10%) is unknown, this indicates that the reporting rates computed by IFPMA based on the DAWN and the exposure data are roughly consistent with the corresponding figures computed by the US government. On this basis, one could conclude that tramadol is similar to codeine (and propoxyphene) in the rate of ED mentions, but lower than hydromorphone which is a Schedule I narcotic drug. Comparison with anti-depressants (amitriptyline and fluoxetine) or anxiolytic drugs such as chlordiazepoxide would not provide any useful information, since these drugs are often prescribed for patients with depression. Because DAWN overdose cases are often associated with suicide attempts which frequently occur in depressed patients, it is natural that these drugs are mentioned more frequently in emergency departments than drugs of other groups. However, according to the manufacturer Grünenthal Chemie also 50% of tramadol cases are associated with suicide.

In the USA were 645 - 2329 abuse related emergency departments (ED) visits yearly (1995-2002). Also there is an increase in abuse related deaths from 45 (1997) to 88 (2002). These data reflect tramadol only (i.e., any drug reported to DAWN as tramadol, tramadol hydrochloride or Ultram) and did not include paracetamol-tramadol (reported to DAWN as Ultracet). According to DAWN, paracetamol-tramadol was involved in an estimated 440 drug misuse/abuse ED visits in the second half of 2003 in the coterminous U.S.

Until 2002, the Drug Abuse Warning Network ("old" DAWN) collected data only for drug abuse-related ED visits. According to DAWN, there were no drug abuse-related ED visits that involved paracetamol-tramadol from 1995 to 2001, and there were insufficient data to produce a reliable estimate for 2002. (Table 3). The estimates in this table include all ED visits where tramadol or paracetamol-tramadol was present, regardless of whether other drugs also were present.

Drug	1995 ¹	1996	1997	1998	1999	2000	2001 ³	2002
Tramadol	645 ²	1290	1418	1972	1113	1810	2329	1714
Paracetamol-tramadol	0	0	0	0	0	0	0	...

Table 3. DAWN (Drug Abuse Warning Network) Estimate of Tramadol Mentions in Drug Abuse-Related ED Visits in the Coterminous US: 1995-2002* (Old DAWN)

1 Tramadol approved for marketing

2 Refers to an eight months period

3 Paracetamol-tramadol approved for marketing.

Three dots (...) indicate that an estimate with a relative standard error (RSE) greater than 50% has been suppressed.

*Source: Substance Abuse and Mental Health Services Administration, Office of Applied Studies, Drug Abuse Warning Network.

Until 2002, "old" DAWN only collected data only for drug abuse-related deaths. There were no reports of paracetamol-tramadol in drug abuse-related deaths in the consistent panel areas from 1997 to 2002. The

⁴ *DAWN methodology:* New DAWN: The estimates provided from new DAWN include all drug misuse/abuse ED visits that involved the drug of interest, regardless of whether other drugs were involved in the ED visit.

Old DAWN: The estimates from old DAWN include all drug abuse-related ED visits where the drug of interest was present, regardless of whether other drugs were present in the ED visit. Similarly, the mortality data from old DAWN include all reports of the drug of interest in drug abuse-related deaths, regardless of whether other drugs were present.

next table reflects this finding. The data in this table 4 include all deaths where tramadol or paracetamol-tramadol was reported, regardless of whether other drugs also were present.

Drug	1997	1998	1999	2000	2001 ²	2002
Tramadol	45	46	58	72	86	88
Paracetamol-tramadol	0	0	0	0	0	0

Table 4. Drug Abuse Warning Network (DAWN)*: Drug Abuse-Related Deaths Involving Tramadol from a Consistently Reporting Panel¹ of Medical Examiners: 1997-2002

¹ Deaths reported by a consistent panel of medical examiners in 28 metropolitan areas. Consistent panels include only those jurisdictions that reported at least 10 months of data each year from 1997-2002. The panel does not include New York City (which did not submit data for 2001) or Los Angeles (which did not submit data for 2002).

² paracetamol-tramadol approved for marketing.

*Source: Substance Abuse and Mental Health Services Administration, Office of Applied Studies, Drug Abuse Warning Network.

According to one of the manufacturers, the rates of DAWN mentions for tramadol have been relatively stable since 1996 over the whole observation period averaging to 15 DAWN mentions per 100,000 and ranging from 9.9 to 18.5 DAWN mentions per 100,000 prescriptions, suggesting that there is no increase in citations in the DAWN network over time which in term means no increased risk to potentially suffer intoxications from tramadol. However, over the years the exposure of the US population to tramadol has continuously increased.

The National Survey on Drug Use and Health (NSDUH) reported that the non-medical use of tramadol increased from 52,000 in 2002 to 186,000 in 2003. Around 1.3 million (0.5 percent) persons aged 12 or older have used tramadol products nonmedically in their lifetime. No data is available on current use. The NSDUH also reported that since 2004, approximately 1.3 million (0.5 percent) persons aged 12 or older have used tramadol products nonmedically in their lifetime.

Newer data from the US abuse monitoring system through December 2003 have become available in the meantime also cited in the draft assessment reports as [108]. Updated numbers of rate of abuse/dependence are presented in figure 3.

The solid line in this figure represents the total rate reported (including reports proactively collected by the ISC through their information network), while the dotted line represents the spontaneous reporting rate.

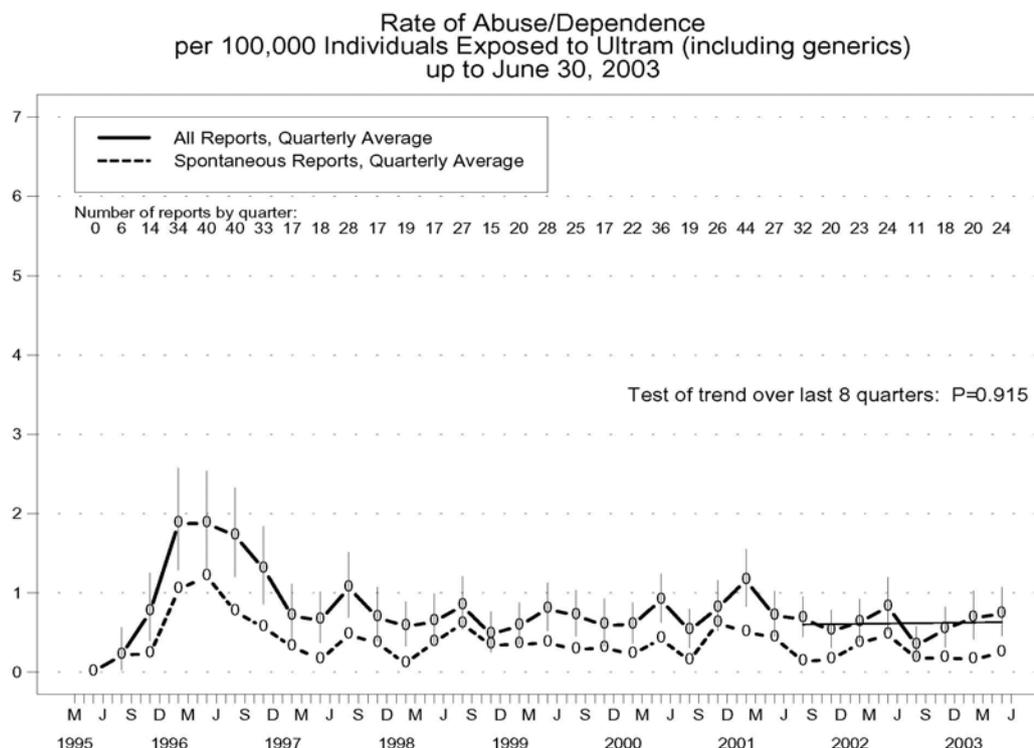
After the first year of launch, monthly patient exposure to tramadol reached approximately 700,000 new patients per month and close to 400,000 continuing patients per month. The general trends in new, continuing, and total tramadol exposures have been consistent over the first 7 years of availability in the US. The availability of ULTRACET[®] (tramadol/acetaminophen) in August 2001 and of generic tramadol in June 2002 has decreased the exposure to branded tramadol ULTRAM[®].

From April 1995 to June 30, 2002, the Independent Steering Committee collected a total of 1,920 reports (spontaneous reports and actively collected reports). Only 688 of these reports were assessed by the ISC to be positive or possible cases of tramadol abuse/dependence; a further 294 reports were classified as "alleged" for abuse as they did not represent abuse in the strict diagnostic criteria. Another 601 cases referred to withdrawal alone with no indication of abuse.

Reports of abuse of tramadol reached an expected peak in the first three quarters of 1996 of approximately 2-3 cases per month per 100,000 patients as a result of tramadol's US launch in 1995. Subsequently, the rate decreased to an average of less than 1 case per 100,000 patients.

This data does show that reporting rates for abuse/dependence still remain stable below 1 case per 100,000 patients (Figure 1). Basically numbers did not really change since 1997.

Figure 1:



Response to the WHO questionnaire

Of the 85 countries which indicated medical use of tramadol in response to the WHO Questionnaire, the following 21 countries reported some abuse: Australia, Chile, China, Costa Rica, France, Georgia, Iceland, Iran, Ireland, Jordan, Lithuania, Macedonia, Mauritius, Poland, Spain, Sweden, Switzerland, Ukraine and the USA.

Those with some indication of the extent of the problem are summarized below.

Australia: sporadic abuse, insufficient to warrant further regulation

Belgium: 17 cases of problematic use in the pharmacovigilance database.

China: some heroine addicts use tramadol as a surrogate

Costa Rica: 8-12 cases per year (2004-2005) of which 3 cases are moderate to severe dependence acc to ICD-10

France: a number of abuse cases (about 65) is reported, which is relatively small to the turnover of tramadol. There are 24 reports of withdrawal symptoms. No death cases reported caused by abuse; 5 caused by overdose, of which 4 are overdose in combination with use of benzodiazepines. 0.5 - 1.0% prescriptions are falsified; some diversion of prescribed medicine to black market.

Iceland: minor abuse only

Iran: a few cases are reported

Ireland: 50-60 cases noted

Mauritius: used as substitute for heroin as to self-treat withdrawal pain and as an adjuvant to misuse of psychotropics. There is no statistic evidence of the extent, except that imports quadrupled since 2000. Before scheduling in 1998 abuse was formidable.

Poland: There is abuse of tramadol, but it abuse is not popular. Abuse is rare.

Sweden: a major drug laboratory encounters tramadol in blood samples of suspected users regularly

Switzerland: 33 (4%) cases out of 843 exposure cases were abuse related; 15 out of 33 were multidrug exposures.

Ukraine: abuse is widespread

USA: as mentioned above.

Data from Uppsala Monitoring Centre (UMC): *As of May 2002*, the UMC database (Communication from Uppsala Monitoring Centre to WHO Secretariat, received in June 2002) has 252 reports of "drug abuse", 414 reports of "drug dependence" and 452 reports of "withdrawal syndrome", reported as ADRs to tramadol. After flunitrazepam, tramadol ranks second in the list of drugs for which "drug abuse" has been reported, 5th in the list of "drug dependence", and 6th in the list of "withdrawal syndrome". In all the three lists, tramadol ranks higher than any other drugs used for the treatment of pain except butorphanol, which tops the list of drugs for which "drug dependence" has been reported. A large proportion of these abuse-related ADR reports originates from the USA, where the drug has been on the market since 1995 (240/252 of "drug abuse"; 348/414 of "drug dependence"; 298/452 of "withdrawal syndrome"). In other words, it is the US reports which have pushed tramadol up in the ranking of drugs for which abuse-related ADRs have been reported to UMC after its initial pre-review by the Committee in 1992.

With regard to medical use of tramadol, the IFPMA report [89] shows a 10-fold increase in the global consumption of tramadol from 13.8 tons in 1993 to 149 tons in 2000. Although the US consumption is rapidly increasing since its marketing in 1995, Europe remains to be the main consumer, consuming more than double the quantity prescribed in the USA in 2000. Consumption in the rest of the world is less than 10% of the global consumption. In view of this, the predominance of US reports described in the preceding paragraph could merely be a reflection of the higher reporting rates for newer drugs, as suggested by IFPMA. The IFPMA report [89] indicates that the reporting rates were higher during the first several years after its marketing in Germany, UK and USA. This is a usual phenomenon in spontaneous reporting of ADRs, since unknown/new ADRs receive priority attention of reporting doctors. The lower initial reporting rates of France as compared with the initial reporting rates of the other three countries in the IFPMA report, may be due to a genuine inter-country difference in reporting rates or to the fact that these ADRs were already well known by the time tramadol was placed on the French market, or to both. In general, a reduction in reporting rates of an ADR with time does not necessarily signify a real reduction in the rate of occurrence of the ADR.

One could also argue that, because all drugs are "new" at one time in all countries, looking at the US data differently from the others is unjustified. However, it should be stressed that the growth rate of US consumption of tramadol was exceptionally high during the first 5 years of marketing, at the average rate of over 7 tons per year. This is 10 times greater than the average annual growth rate of European consumption between 1977 and 1993, according to a calculation based on the consumption data given in the IFPMA report [89]. The report, for example, presents a graph showing changes in the sales of tramadol and the number of abuse-related ADR reports received every year in Germany. The very slow pace of initial growth in German consumption may be associated with the cautious marketing strategy of Grünenthal which developed the drug. In contrast, the US market is highly competitive where direct-to-consumer promotion of prescription drugs is allowed. The very rapid increase in tramadol consumption in the USA has occurred under these circumstances, during the period of time when ADR reporting rates are generally high. This might justify a separate assessment of the US abuse-related ADR reports.

Without the US figures, tramadol moves down to below buprenorphine on two of the three lists, namely "drug abuse" (12 for tramadol, 78 for buprenorphine) and "drug dependence" (66 for tramadol, 117 for buprenorphine). It remains higher than buprenorphine in the list for "withdrawal syndrome", with the ratio of 154 to 88. In terms of exposure, it is noted that the global consumption patterns of tramadol [89] and buprenorphine [91] indicate a similar curve, showing a steady but not a rapid increase initially, followed by a sharp increase in recent years. In 1993, the global buprenorphine consumption was 48 kg or 38 million DDDs, according to the statistics of the INCB, when tramadol consumption was 13.8 tons or 46 million DDDs. In other words, global exposure to tramadol was slightly larger than to buprenorphine in terms of DDDs until 1993. Buprenorphine consumption grew a little faster than tramadol after 1993, to 1.124 tons (940 million DDDs) in 2000, while tramadol consumption went up to 149 tons (excluding the USA, 106 tons or 354 million DDDs). US consumption of buprenorphine is ignored as it has never exceeded 2 % of

the global consumption, as calculated from the INCB statistics on global consumption and the DEA statistics on importation.

Thus, buprenorphine consumption as indicated in DDDs overtook that of tramadol after 1993, widening the gap to almost 1 to 3 by 2000. However, its impact in terms of real exposure may be negligible since the sharp increase in buprenorphine consumption in recent years is due to the rapid increase in its use for the treatment of opioid dependence. The actual average daily dose of buprenorphine as used for this purpose in France is reported to be 11.5 mg or almost 10 times the DDD for analgesic use [92]. Therefore, for the purpose of measuring the level of exposure to the drug in terms of DDDs, it is not appropriate any more to apply 1.2 mg/day, which is a figure derived from its use as an analgesic. To be able to accurately convert the consumed weight of buprenorphine into DDDs, it is necessary to find out the precise percentage of buprenorphine used for pain and that used for the treatment of dependence. Such data are not available. Nevertheless, the figures mentioned above would provide a sufficient basis to estimate that the recent exposure to buprenorphine in terms of real DDDs would be roughly comparable to that of tramadol, even though buprenorphine consumption in weight is growing faster than that of tramadol in recent years.

Coupled with the overall similarity in the pattern of consumption before 1993, the total cumulative exposure to the two drugs (excluding the USA) could also be estimated to be roughly equivalent in DDDs. Taking this into account, a comparison between tramadol and buprenorphine in terms of reporting rates of abuse-related ADRs to UMC (excluding the data from USA) would suggest that "drug abuse" and "drug dependence" may be less likely to be reported for tramadol but "withdrawal syndrome" is more likely to be reported for it. However, the US reports are distinct from the corresponding data from other countries. In the US data, the numbers of "drug abuse" and "drug dependence" reports relative to that of "withdrawal syndrome" are both much larger than the non-US data, as discussed in more detail later in this section.

As of December 2005, out of a global database of 22753 reported adverse effects, the UMC reported, as far as it concerns dependency related adverse effects: 2 cases of tolerance (0.008 %), 22 cases of increased tolerance (0.09 %), 593 cases of withdrawal syndrome (2.6 %), 2 cases of withdrawal convulsions (0.008%), 303 cases of drug abuse (1.3 %) and 492 cases of drug dependence (2.2 %) (unpublished, communication to WHO, 2005).

Post-marketing surveillance data from Germany As discussed in section 11, Germany had long been the main consumer country of tramadol in the world. Consuming 85 million DDDs, the country still accounted for 65% of the world's consumption of the drug in 1993 [89]. The IFPMA report analyses the abuse-related ADR reports collected by Grünenthal in relation to the sales data. The reporting rate was the highest in 1980 (4th year of marketing), which gradually came down with time, even though tramadol was not subject to any special control measures in Germany. It is interesting to compare these data with the figures from the WHO ADR database. Because of the time lag between the time an ADR is detected at the national level and the time the data are entered into the international ADR database of UMC, national figures are usually larger than those received by UMC from that country. In this particular case, however, the gap is so significant that it is difficult to explain it by the time lag theory alone. For example, UMC data from Germany has 21 reports of "drug dependence" while the figure from Grünenthal is 10 times larger (212). For "drug abuse", 57 according to Grünenthal, 9 only in the WHO database. The difference is smaller but still quite significant for "withdrawal syndrome" (44 according to Grünenthal, 17 in the WHO database). The Grünenthal figures are much larger than the corresponding numbers in the WHO database for USA, France, Sweden and a few other countries but not for the United Kingdom. It may be fair to say that the Grünenthal database on tramadol is more comprehensive than the ADR data received by UMC.

8. Nature and magnitude of public health problems

As described in Sections 10 and 11, tramadol is used therapeutically in over 100 countries at present but its consumption outside Europe and the USA is still quite limited (less than 10%). As anticipated from this, cases of abuse have mainly been reported in the United States and Europe. Tramadol misuse/overdose or

concomitant use of other drugs have resulted in some hospital admissions and deaths. Any toxic effects are produced directly from the drug and the presence of other drugs (in particular CNS depressants and monoamine uptake inhibitors) may exacerbate such effects.

9. National controls

The IFPMA report [89] indicates that out of the 104 countries where tramadol is marketed, tramadol is only a prescription drug in 75 of them, additional controls being required in the remaining 29 countries. If this information is correct, one would assume that placing tramadol under international control would have little impact on its availability in these 29 countries which already control tramadol. In contrast, in the other 75 countries without additional controls at present, the international control decision would be expected to have some negative impact on its availability.

18 Out of 69 countries answered in response to the WHO Questionnaire, that the international control of tramadol would reduce its availability for medical use.

The countries that indicated the decreased availability explained this as follows:

Australia: there will be some impact on its medical availability; minor regulatory burden and additional controls on supply and distribution.

China: it will change the mode of circulation, thereby affecting its medical availability

Macedonia: patients will need two prescriptions and more requirements will be made to pharmacies

Poland: restriction because of storage and administrative requirements

Sweden: due to special procedures

Cambodia: it will impact its medical access for the patient

India: it will restrict its medical availability

Japan: it will impact its medical availability and doctors will not tolerate the inconvenience

Myanmar: it will become limited in its medical availability, especially in remote areas of the country and in places where professionals authorized to prescribe them are not available.

Thailand: placing under international control will cause shortage and price will be higher. The consumer will get the economic impact if medicine is expensive.

Bangladesh: it will take more time than before and due to the two-tier system it will hamper its medical availability

Ecuador: it will restrict the prescribing and make the distribution more difficult

United Arab emirates: it may interfere with easy use for proper medical indication

Egypt supposed a mechanism that may improve access for medical purposes: the control may stop diversion to black market, so that the availability will become better for real patients (note: this is a mechanism opposite to the mechanism supposed by Egypt for buprenorphine)

Ukraine remarked that international control will reduce the number of users and the abuse of the substance.

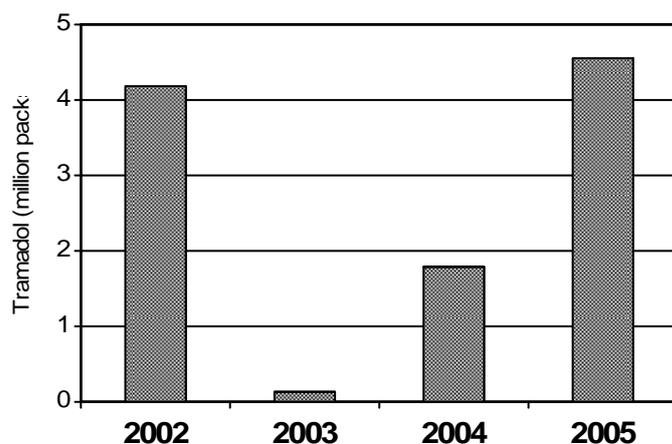
Without any doubt increased national control would affect availability of tramadol in a negative way, in many countries probably extremely so.

Although it was supposed that control in Egypt would increase the availability of tramadol for real patients, Egypt is in fact a good example to show how increased national control would probably affect availability for patients in many more countries.

The Egyptian government had decided to schedule tramadol in 2002 and made tramadol available again via the normal Egyptian prescription status as of 2004.

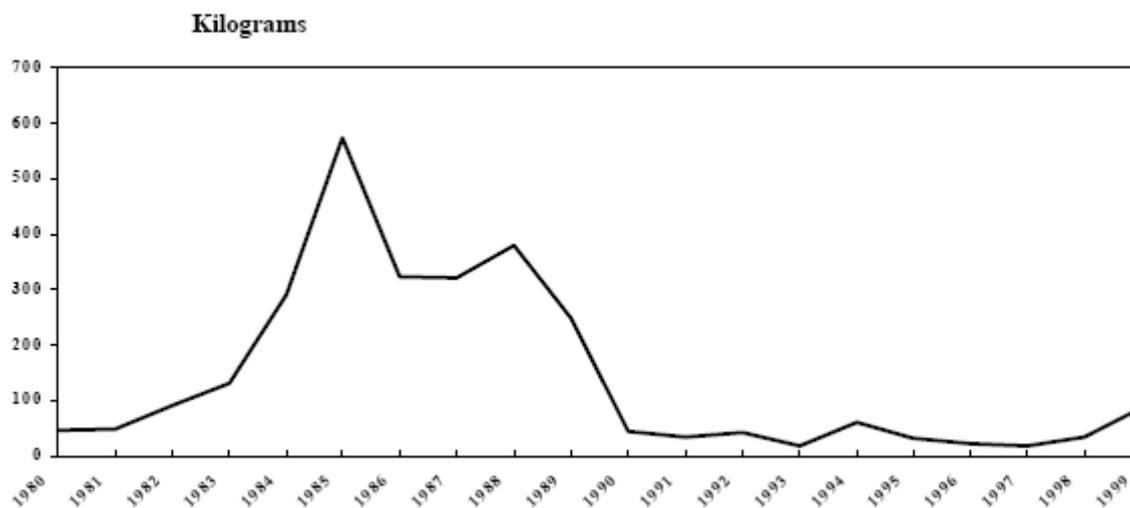
Based on IMS data which were derived from market audits that are monitoring unit sales sold to retail pharmacies and (partly) hospitals, tramadol consumption for medical use decreased dramatically after scheduling. The consumption subsequently turned back to the previous level after changing the control status 2 years later (see Figure 2).

Figure 2: Tramadol consumption in Egypt



Another example for impact on availability of scheduled substances is India where the morphine consumption decreased dramatically after scheduling (see figure 3).

Figure 3: Morphin consumption in India



from: WHO Collaborating Centre for Policy and Communications in Cancer Care

10. Therapeutic and industrial use

Tramadol hydrochloride has been used as an analgesic since the 1970s and was in 2002 currently used in 104 countries according to IFPMA [89]. Of the 100 countries which have responded to the WHO Questionnaire in 2002, 85 reported the marketing of tramadol for pain. After 2002 tramadol was introduced in another number of countries. In the 2005 questionnaire 96% of the countries reported its medical use. Taking into account the response rate to the WHO Questionnaire, this result appears to be consistent with the information from the IFPMA. No industrial use has been reported.

Different preparations of tramadol hydrochloride exist (tablets, capsules, syrups, injections, suppositories). The defined daily dose (DDD) is 300 mg.

11. Production, consumption and international trade

The IFPMA data [89] show a gradual increase in sales since its marketing in Germany in 1977. In 1993, Germany alone consumed about 65% of the world's consumption of 13.7 tons. The pace of growth in tramadol consumption picked up since then. There was a ten-fold increase in the global consumption of tramadol to over 149 tons in 2000. Although the US consumption is rapidly increasing after its marketing began in 1995, Europe remains to be the main consumer, consuming more than double the quantity prescribed in the USA in 2000. Within Europe, Germany remains to be the main user, still accounting for more than a quarter of the European consumption of 93.4 tons in 2000. The rest of the world consumed less than 10% of the global consumption in 2000.

IMS data provided by the FDA show an increase from 50 mln DDD in 1994 to about 500 mln DDD in 2000 and to over 800 mln DDD in 2004.

Although the absolute consumption of tramadol in Far East, Africa/Asia, Australia/New Zealand, and Latin America is still lower in comparison to Europe and North America these regions have seen a considerable increase of tramadol use coming from low levels.

The increase of tramadol consumption from 2003 to 2004 was in Europe +9%, USA +17%, Far East +24%, Latin America +19%, Australia/New Zealand +16%, and in Africa/Asia an outstanding growth of +58% caused by several countries, e.g. India with its large population number.

Tramadol hydrochloride is produced by various pharmaceutical companies worldwide. International trade data was not made available for this report.

12. Illicit manufacture, illicit traffic and related information

There are no reports of illicit manufacture. Several countries indicated minor seizures of tramadol in response to the WHO Questionnaire, and some smuggling and diversion. In addition, France reported that 0.5 - 1.0% prescriptions are falsified. In the USA tramadol is responsible for 0.8 - 1.0% of selected drug seizures from the National Forensic Laboratory Information System (NFLIS) (years 2000 -2004).

13. International controls in place and their impact

Tramadol is not subject to international control at present. Since most of the opioid analgesics are under international control, it may be necessary to consider the impact of the absence of international control of tramadol on the therapeutic use of analgesic medications in general. As the IFPMA data [89] indicated, tramadol consumption increased more than 10 times between 1993 and 2000. The pace of growth in tramadol consumption was much higher than the fastest growing opioid analgesic, fentanyl, the consumption of which increased about 5 times during the same period [90]. Although buprenorphine consumption grew a little faster than tramadol during the same period, the increase is mostly attributed to its use for the treatment of opioid dependence, as discussed in section 7. Within the group of analgesic drugs, it would be difficult to explain such a rapid increase in tramadol consumption without considering its "regulatory advantage" on the competitive market for analgesic drugs. In countries where opiate analgesics are difficult to use/obtain, there is a problem of overly stringent regulations as documented by INCB [94]. If tramadol were controlled internationally, patients would get equal difficulties to obtain tramadol as they already have in obtaining other opioid pain medication. (See also under 9. for detailed impact of scheduling as expected by the countries).

14. References

1. W. Lintz and H. Uragg.
Quantitative determination of tramadol in human serum by gas chromatography-mass spectrometry, *J. Chrom.*, Vol 341: 65-79, 1985.
2. R. Becker and W. Lintz.
Determination of tramadol in human serum by capillary gas chromatography with nitrogen-selective detection, *J. Chrom.*, Vol 377: 213-220, 1986.
3. M. Nobilis et al.
High-performance liquid chromatographic determination of tramadol in human plasma, *J. Chrom.*, Vol 681: 177-183, 1996.
4. M. J. Bogusz, R. D. Maier, K. D. Kruger and U. Kohls.
Determination of common drugs of abuse in body fluids using one isolation procedure and liquid chromatography-atmospheric-pressure chemical-ionization mass spectrometry, *J. Anal. Toxicol.*, Vol 22: 549-558, 1998.
5. E. A. Shipton.
Tramadol – present and future, *Anaesth. Intensive Care*, Vol 28: 363-374, 2000.
6. T. A. Bamigbade and R. M. Langford.
Tramadol hydrochloride: an overview of current use, *Hosp. Med.*, Vol 59: 373-376, 1998.
7. L. J. Scott and C. M. Perry.
Tramadol – a review of its use in perioperative pain, *Drugs*, Vol 60 (1): 139-176, 2000.
8. C. R. Lee, D. McTavish and E. M. Sorkin.
Tramadol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states, *Drugs*, Vol 46: 313-340, 1993.
9. P. Dayer, J. Desmeules and L. Collart.
Pharmacology of tramadol, *Drugs*, Vol 53 Suppl 2: 18-24, 1997.
10. T. A. Bamigbade, C. Davidson and R. M. Langford.
Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus, *Br. J. Anaes.*, Vol 79: 352-3356, 1997.
11. S. Grond, T. Meuser, D. Zeuch et al.
Analgesic efficacy and safety of tramadol enantiomers in comparison with the racemate: a randomised, double-blind study with gynaecological patients using intravenous patient-controlled analgesia, *Pain*, Vol 62: 313-320, 1995.
12. C. Gillen, M. Haurand, D. J. Kobelt and S. Wnendt.
Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor, *Naunyn Schmiedebergs Arch. Pharmacol.*, Vol 362 (2): 116-121, 2000.
13. K. S. Lewis and N. H. Han.
Tramadol: a new centrally acting analgesic, *Am. J. Health-Syst. Pharm.*, Vol 54: 643-652, 1997.
14. K. A. Lehmann, U. Kratzenberg, B. Schroeder-Bark et al.
Postoperative patient-controlled analgesia with tramadol: analgesic efficacy and minimum effective concentrations, *Clin. J. Pain*, Vol 6 (3): 212-220, 1990.
15. R. J. M. Houmes, M. A. Voets, A. Verkaaik et al.
Efficacy and safety of tramadol versus morphine for moderate to severe postoperative pain with special regard to respiratory depression, *Anesth. Analg.*, Vol 74 : 510-514, 1992.
16. M. D. Vickers, D. O'Flaherty, S. M. Szekely et al.
Tramadol: pain relief by an opioid without depression of respiration, *Anesthesia*, Vol 47: 291-296, 1992.
17. P. Tarkkila, M. Tuominen and L. Lindgren

- Comparison of respiratory effects of tramadol and oxycodone, *J. Clin. Anesth.*, Vol 9: 582-585, 1997.
18. A. T. Bosenberg and S. Ratcliffe.
The respiratory effects of tramadol in children under halothane anaesthesia, *Anaesthesia*, Vol 53 : 960-964, 1998.
19. J. Schaffer, S. Piepenbrock, F. J. Kretz et al.
Nalbuphine and tramadol for control of postoperative pain in children, *Anaesthesist*, Vol 35: 408-413, 1986.
20. Ortho-McNeil Pharmaceuticals.
Ultram package insert, 1995.
21. M. Cossmann and K. M. Wilsmann.
Effect and side effects of tramadol: an open phase IV study with 7198 patients, *Therapiewoche*, Vol 37: 3475-3485, 1987.
22. A. Manocha, K. K. Sharma and P. K. Mediratta.
Tramadol, a centrally acting opioid: anticonvulsant effect against maximal electroshock seizure in mice, *Indian J. Physiol. Pharmacol.*, Vol 42: 407-411, 1998.
23. P. O. Prasertsawat, Y. Herabutya and K. Chaturachinda.
Obstetric analgesia: comparison between tramadol, morphine and pethidine, *Curr. Ther. Res.*, Vol 40: 1022-1028, 1986.
24. R. Worz.
Control of cancer pain with analgesics acting in the central nervous system, *Recent Results Cancer Res.*, Vol 89: 100-106, 1984.
25. J. L. De Witte, J. S. Kim, D. I. Sessler et al.
Tramadol reduces the sweating, vasoconstriction and shivering thresholds, *Anesth. Analg.*, Vol 87: 173-179, 1998.
26. P. Mathivet et al.
Binding characteristics of GHB as a weak but selective GABA_B receptor agonist, *Eur. J. Pharmacol.*, Vol 321: 67-75, 1997.
27. H. Potschka, E. Friderichs and W. Loscher.
Anticonvulsant and proconvulsant effects of tramadol, its enantiomers and its M1 metabolite in the rat kindling model of epilepsy, *Br. J. Pharmacol.*, Vol 131: 203-212, 2000.
28. The Merck Index.
Tramadol in "The Merck Index, 10th Edition", Merck and Co., Rahway, USA, p 1368, 1983.
29. T. Matthiesen, T. Wohrmann, T. P. Coogan and H. Uragg.
The experimental toxicology of tramadol: an overview, *Toxicol. Lett.*, Vol 95: 63-71, 1998.
30. T. Yanagita.
Drug dependence potential of 1-(m-methoxyphenyl)-2-(dimethylaminomethyl)-cyclohexan-1-ol hydrochloride (tramadol) tested in monkeys, *Drug. Res.*, Vol 28 (1): 158-163, 1978.
31. Ortho-McNeil Pharmaceuticals.
Ultram package insert, 2000.
32. H. A. Spiller, S. E. Gorman, D. Villalobos et al.
Prospective multicenter evaluation of tramadol exposure, *J. Toxicol. Clin. Toxicol.*, Vol 35: 361-364, 1997.
33. B. J. Mason and K. H. Blackburn.
Possible serotonin syndrome associated with tramadol and sertraline coadministration, *Ann. Pharmacother.*, Vol 60: 636-644, 1996.
34. S. Kesavan and G. M. Sobala.
Serotonin syndrome with fluoxetine plus tramadol, *J. R. Soc. Med.*, Vol 92 (9): 474-475, 1999.
35. M. G. Ripple, J. P. Pestaner, B. S. Levine and J. E. Smialek.

Lethal combination of tramadol and multiple drugs affecting serotonin, *Am. J. Forensic Med. Pathol.*, Vol 21 (No. 4): 370-374, 2000.

36. T. A. Bamigbade and R. M. Langford.

The clinical use of tramadol hydrochloride, *Pain Reviews*, Vol 5: 155-182, 1998.

37. K. L. Preston, D. R. Jasinski and M. Testa

Abuse potential and pharmacological comparison of tramadol and morphine, *Drug Alcohol Depend.*, Vol 27: 7-17, 1991.

38. L. Collart, C. Luthy and P. Dayer.

Partial inhibition of tramadol antinociceptive effect by naloxone in man, *Br. J. Pharmacol.*, Vol 35: 73, 1993.

39. K. E. Goeringer, B. K. Logan and G. D. Christian.

Identification of tramadol and its metabolites in blood from drug-related deaths and drug-impaired drivers, *J. Anal. Toxicol.*, Vol 21: 529-537, 1997.

40. S. P. Elliott.

Non-fatal instances of tramadol intoxication, unpublished findings, 2002.

41. D. K. Sachdeva and B. T. Jolly.

Tramadol overdose requiring prolonged opioid antagonism, *Am. J. Emer. Med.*, Vol 15: 217-218, 1984.

42. F. Riedel and H. B. Von Stockhausen.

Severe cerebral depression after intoxication with tramadol in a 6 month old infant, *Eur. J. Clin. Pharm.*, Vol 26: 631-632, 1984.

43. J. D. Tobias.

Seizure after overdose of tramadol, *South Med. J.*, Vol 90 (8): 826-827, 1997.

44. M. G. Bianchetti, A. Beutler and P. E. Ferrier.

Acute poisoning with a narcotic (tramadol) in an infant of five weeks, *Helv. Paediatr. Acta.*, Vol 43 (3): 241-244, 1988.

45. N. Edwards.

“The work of the NPIS”, presentation at LTG toxicology meeting, London, 2002.

46. SAMHSA, Drug Abuse Warning Network.

Annual DAWN report, 2000-2001.

47. K. J. Lusthof and P. G. M. Zweipfenning.

Suicide by tramadol overdose, *J. Anal. Toxicol.*, Vol 22: 260, 1999.

48. K. A. Moore, S. J. Cina, R. Jones, D. M. Selby, B. Levine and M. L. Smith.

Tissue distribution of tramadol and metabolites in an overdose fatality, *Am. J. Forensic Med. Pathol.*, Vol 20: 98-100, 1999.

49. F. Musshoff, B. Madea.

Fatality due to ingestion of tramadol alone, *Forensic Sci. Int.*, Vol 116: 197-199, 2001.

50. K. Michaud, M. Augsburg, N. Romain, C. Giroud and P. Mangin.

Fatal overdose of tramadol and alprazolam, *Forensic Sci. Int.*, Vol 105: 185-189, 1999.

51. A. F. Hernandez, M. N. Montero, A. Pla and E. Villanueva.

Fatal moclobemide overdose or death caused by serotonin syndrome, *J. Forensic Sci.*, Vol 40: 128-130, 1995.

52. S. P. Elliott.

22 Fatal instances of tramadol intoxication, unpublished findings, 2005.

53. S. Hazelhurst.

2 Fatal instances of tramadol intoxication, LGC Ltd, personal communication, unpublished findings, 2002.

54. R. Wennig, G. Asselborn and M. Yegles.
“Chronic multiple drug abuse with suicidal endpoint”, presented at the annual meeting of The International Association of Forensic Toxicologists (TIAFT), 1997.
55. S. Liao et al.
The effect of food on the bioavailability of tramadol, *Pharm. Res.*, Vol 9: 308, 1992.
56. R. H. De Jong.
Comment on the hypoalgesic effect of tramadol in relation to CYP2D6, *Pain Dig.*, Vol 7 (4): 245, 1997.
57. W. D. Paar, S. Poche, J. Gerloff et al.
Polymorphic CYP2D6 mediates O-desmethylation of the opioid analgesic tramadol, *Eur. J. Clin. Pharmacol.*, Vol 53: 235-239, 1997.
58. W. D. Paar, P. Franjus and H. J. Dengler.
The metabolism of tramadol by human liver microsomes, *Clin. Investig.*, Vol 70: 708-710, 1992.
59. L. Poulsen, L. Arendt Nielsen, K. Brosen and S. H. Sindrup.
The hypoalgesic effect of tramadol in relation to CYP2D6, *Clin. Pharmacol. Ther.*, Vol 60: 636-644, 1996.
60. W. Lintz, H. Beier and J. Gerloff.
Biotransformation of tramadol in man, *Drug Res.*, Vol 31: 1932-1943, 1981.
61. S. Liao, J. F. Hills, R. K. Nayak et al.
Pharmacokinetics of tramadol following single and multiple oral doses in man, *Pharm. Res.*, Vol 9: 308, 1992..
62. W. Lintz, H. Barth, G. Osterloh et al.
Bioavailability of enteral tramadol formulations, *Drug Res.*, Vol 36: 1278-1283, 1986.
63. M. O. Rojas-Corrales, J. Gilbert-Rahola and J. A. Mico.
Tramadol induces antidepressant-type effects in mice, *Life Sci.*, Vol 63 (12): 175-180, 1998.
64. H. F. Miranda and G. Pinardi.
Antinociception, tolerance, and physical dependence comparison between morphine and tramadol, *Pharmacol. Biochem. Behav.*, Vol 61 (4): 357-360, 1998.
65. E. Friedrichs, E. Felgenhauer, P. Jongschapp and G. Osterloh.
Pharmacological investigations on analgesia and the development of dependence and tolerance with tramadol, a strongly acting analgesic, *Drug Res.* Vol 28: 122-134, 1978.
66. T. Murano, H. Yamamoto, Y. Endo, N. Okada, Y. Masuda and I. Yano.
Studies of dependence on tramadol in rats, *Drug Res.* Vol 28: 152-158, 1978.
67. J. F. Coetzee, J. S. Maritz and J. C. Du Toit.
Effect of tramadol on depth of anaesthesia, *Br. J. Anaesth.*, Vol 76: 415-418, 1996.
68. T. A. Bamigbade, R. M. Langford, A. L. Blower et al.
Pain control in day surgery: tramadol compared to standard analgesia, *Br. J. Anaesth.*, Vol 80: 558-559, 1998.
69. M. A. Pluim, J. T. Wegener, J. Ruprecht and A. G. Vulto.
Tramadol suppositories are less suitable for post-operative pain relief than rectal acetaminophen/codeine, *Eur. J. Anaesthesiol.*, Vol 16: 473-478, 1999.
70. R. L. Rauck, G. E. Rouff and J. I. McMillen.
Comparison of tramadol and acetaminophen with codeine for long-term pain management in elderly patients, *Curr. Ther. Res.*, Vol 55: 1417-1431, 1994.
71. E. M. Jensen and F. Ginsberg.
Tramadol versus dextropropoxyphene in the treatment of osteoarthritis, *Drug Invest.*, Vol 8: 211-218, 1994.
72. S. H. Roth.
Efficacy and safety of tramadol HCl in breakthrough osteoarthritis pain, *J. Rheumatol.*, Vol 25: 1358-1363, 1998.

73. S. Nossol.
Treatment of pain with sustained-release tramadol, *Int. J. Clin. Pract.*, Vol 52: 94-126, 1998.
74. J. Sorge and T. Stadler.
Comparison of the analgesic efficacy and tolerability of tramadol 100 mg sustained-release tablets and tramadol 50 mg capsules for the treatment of chronic low back pain, *Clin. Drug Invest.*, Vol 14: 157-164, 1997.
75. N. A. Osipova, G. A. Novikov, V. A. Beresnev et al.
Analgesic effect of tramadol in cancer patients with chronic pain: a comparison with prolonged-action morphine sulfate, *Curr. Ther. Res.*, Vol 50: 812-821, 1991.
76. A. V. Bono and S. Cuffari.
Effectiveness and tolerance of tramadol in cancer pain. A comparative study with respect to buprenorphine, *Drugs*, Vol 53 Suppl 2: 40-49, 1997.
77. P. Sacerdote, M. Bianchi, L. Gaspani and B. Manfredi.
The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients, *Anesth. Analg.*, Vol 90 (6): 1411-1414, 2000.
78. J. Cami, X. Lamas and M. Farre.
Acute effects of tramadol in methadone-maintained volunteers, *Drugs*, Vol 47 Suppl 1: 39-43, 1994.
79. X. Arknine, I. Varescon-Pousson and A. Boissonnas.
Tramadol dependence in a previous heroin addict, *Ann. Med. Interne (Paris)*, Vol 151 Suppl B: 34-35, 2000.
80. S. L. Nightingale.
Important new safety information for tramadol hydrochloride, *JAMA*, Vol 275: 1224, 1996.
81. T. J. Cicero, E. H. Adams, A. Geller, J. A. Inciardi, A. Munoz, S. H. Schnoll, E. C. Senay and G. E. Woody.
A postmarketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States, *Drug Alcohol Depend.*, Vol 57: 7-22, 1999.
82. Z. M. Liu, W. H. Zhou and Z. Lian.
Drug dependence and abuse potential of tramadol, *Chung Kuo Yao Li Hsueh Pao*, Vol 20 (1): 52-54, 1999.
83. R. J. Leo, R. Narendran and B. De Guiseppe.
Methadone detoxification of tramadol dependence, *J. Subst. Abuse Treat.*, Vol 19: 297-299, 2000.
84. W. R. Yates, M. H. Nguyen and J. K. Warnock.
Tramadol dependence with no history of substance abuse, *Am. J. Psychiatry*, Vol 158: 964, 2001.
85. E. Freye and J. Levy.
Acute abstinence syndrome following abrupt cessation of long-term use of tramadol (Ultram): a case study, *Eur. J. Pain.*, Vol 4 (3): 307-311, 2000.
86. <http://erowid.org>.
87. R. R. Reeves and V. Liberto.
Abuse of combinations of carisoprodol and tramadol, *South Med. J.*, Vol 94 (5): 512-514, 2001.
88. W. Keup.
Missbrauchsmuster bei abh angigkeit von alcohol, medikamenten und drogen: Fruhwarnsystem-daten fur die bundersrepublik Deutschland 1976-1990, Lambertus, Freiburg im Breisgau.
89. International Federation of Pharmaceutical Manufacturers Associations (IFPMA)
Comprehensive Review of Abuse Risk for Tramadol (IFPMA contribution to the 33rd Expert Committee on Drug Dependence), 2002
90. International Narcotics Control Board (INCB)
Narcotic Drugs: estimated world requirements for 2001; statistics for 1999. United Nations, New York, 2001

91. International Narcotics Control Board (INCB)
Psychotropic Substances: statistics for 1999. United Nations, New York, 2001
92. Thirion X, Lapierre V, Micallef J, Ronfle E, Masut A, Coudert C, Mabriez JC, Sanmarco JL. Buprenorphine prescription by general practitioners in a French Region. *Drug and Alcohol Dependence*, Vol 56(2): 197-204, 2002.
93. International Federation of Pharmaceutical Manufacturers Associations (IFPMA)
A review of Data for the Scientific Community in Preparation for the World Health Organization 2002 Critical Review of Buprenorphine (IFPMA contribution to the 33rd Expert Committee on Drug Dependence), 2002
94. International Narcotics Control Board (INCB)
Availability of Opiates for Medical Needs: Special report prepared pursuant to Economic and Social Council resolution 1990/31 and 1991/43. United Nations, New York, 1996
95. M. R. Rouini, Y. H. Ardankani, F. Soltani, H. Y. Aboul-Enein and A. Foroumadi.
Development and validation of a rapid HPLC method for simultaneous determination of tramadol, and its two main metabolites in human plasma. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.*, (in press) 2005.
96. B. R. Close.
Tramadol: does it have a role in emergency medicine? *Emerg. Med. Australas.*, Vol 17 (1): 73-83, 2005.
97. S. D. Silberstein, F. G. Freitag, T. D. Rozen, D. B. Kudrow, D. J. Hewitt, D. M. Jordan, A. C. Fisher and N. R. Rosenthal.
Tramadol/acetaminophen for the treatment of acute migraine pain: findings of a randomised, placebo-controlled trial. *Headache*, Vol 45 (10): 1317-1327, 2005.
98. P. K. Gillman.
Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. *Br. J. Anaesth.*, Vol 95 (4): 434-441, 2005.
99. R. Mahlberg, D. Kunz, J. Sasse and J. Kircheriner.
Serotonin syndrome with tramadol and citalopram. *Am. J. Psychiatry*, Vol 161 (6): 1129, 2004.
100. K. Hedenmalm, J. D. Lindh, J. Sawe and A. Rane.
Increased liability of tramadol-warfarin interaction in individuals with mutations in the cytochrome P450 2D6 gene. *Eur. J. Clin. Pharmacol.*, Vol 60 (5): 369-372, 2004.
101. Drug Abuse Warning Network (DAWN)
Emergency department trends 1995-2002 (published 2003).
102. R. Kronstrand.
A case of repeated tramadol poisoning in an infant. Presented at the American Academy of Forensic Sciences, Chicago, 2003.
103. N. D. Bynum, J. L. Poklis, M. Gaffney-Kraft, D. Garside and J.D. Roper-Miller.
Postmortem distribution of tramadol, amitriptyline, and their metabolites in a suicidal overdose. *J. Anal. Toxicol.*, Vol 29: 401-406, 2005.
104. K. Galer and M. Krzyzanowski.
[Death attributed to toxic interaction of tramadol and other drugs]. *Arch. Med. Sadowej. Kryminol.*, Vol 54 (1): 73-78, 2004.
105. F. Clarot, J. P. Gouille, E. Vaz and B. Proust.
Fatal overdoses of tramadol: is benzodiazepine a risk factor of lethality? *Forensic sci. Int.*, Vol 134 (1): 57-61, 2003.
106. M. B. Loughrey, C. M. Loughrey, S. Johnston and D. O'Rourke.
Fatal hepatic failure following accidental tramadol overdose. *Forensic sci. Int.*, Vol 134 (2-3): 232-233, 2003.
107. J. S. Knisely, E. D. Campbell, K. S. Dawson and S. H. Schnoll.
Tramadol post-marketing surveillance in health care professionals. *Drug and Alcohol Dependence*, Vol 68 (1): 15-22, 2002.

108. T. J. Cicero, J. A. Inciardi, E. H. Adams, A. Geller, E. C. Senay, G. E. Woody and A. Munoz. Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic products: results of an abuse monitoring system, 1994-2004. *Pharmacoepidemiol. Drug Saf.*, Vol 14 (12): 851-859, 2005.
109. E. C. Senay, E. H. Adams, A. Geller, J. A. Inciardi, A. Munoz, S. H. Schnoll, G. E. Woody and T. J. Cicero. Physical dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug and Alcohol Dependence*, Vol 69 (3): 233-241, 2003.
110. J. P. Zacny.
Profiling the subjective, psychomotor, and physiological effects of tramadol in recreational drug users. *Drug and Alcohol Dependence*, Vol 80: 273-278, 2005.
111. Frink, M.Ch., H.H. Hennies, W. Englberger, M. Haurand, and B. Wilffert, 1996, "Influence of Tramadol on Neurotransmitter Systems of the Rat Brain," *Arzneim. Forsch.*,46: 1029-36.
112. Gillen, C., M. Haurand, D. J. Kobelt, and S. Wnendt, 2000, "Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor," *Naunyn-Schmiedeberg's Arch Pharmacol.* 362: 116-121.
113. Collart L, Luthy C, Dayer P. Partial Inhibition of tramadol antinociceptive effect by naloxone in man. *Br J Clin Pharmacol.* 1993;35:73
114. Adams EH et al. A comparison of the abuse liability of tramadol, NSAIDS, and hydrocodone on patients with non-malignant chronic pain. Accepted for publication in *J of Pain and Symptom Management* in 2005.