INTRODUCTION

Tramadol

Tramadol is a centrally acting opioid analgesic used to treat moderate to severe pain as a substitute to codeine. Tramadol is similar to levorphanol with much lower μ-agonism, both agents have serotonin-norepinephrine reuptake inhibitor (SNRI) activity.[1-3] The drug has a wide range of applications, including treatment of rheumatoid arthritis, restless legs syndrome, motor neurons disease and fibromyalgia. It was launched and marketed as Tramal and Ultram.[4-6]

It has been suggested that tramadol could be effective for alleviating symptoms of depression, anxiety, and phobias because of its action on the noradrenergic and serotonergic systems, and thus known as "atypical" opioid activity.[7, 8] However, health professionals have not endorsed its use for these disorders, claiming that it can only be used as a unique treatment when other treatments fail, and must be used under the control of a psychiatrist.[9-12]

Incidence of tramadol overdose

The US Food and Drug Administration (FDA) has received hundreds of reports of tramadol-associated abuse, dependence, and withdrawal syndrome [2]. Tramadol was ranked second to oxycodone in number of exposure cases according to annual reports of the American Association of Poison Control Centers in the 2001 and 2002. [3]

World Health Organization (WHO) paid a great attention to the abuse and dependence of tramadol. From 1992 to 2006, tramadol dependence was evaluated for four times by Expert Committee on Drug Dependence (ECDD) [3-6]. Because the available information was still not enough, The Expert Committee could not decide to control tramadol internationally. Although tramadol abuse is occurring at low-level worldwide, the non-medical purpose use of tramadol was popular in China since its first marketing in the early 1990s as a non controlled analgesic, especially in opiate addicts and adolescents. In order to prevent the abuse of tramadol and manage its clinical application, in 2007, the State Food and Drug Administration of China issued the newest version of measures for psychotropic drugs administration and tramadol was controlled as the second category of psychotropic drugs [7].

According to the report of National Drug Abuse Monitoring, the proportion of tramadol use among drug abusers increased from 0.2% in 2004 to 16.0% in 2006; the trend of tramadol use varied very smoothly from 2007 to 2009; however, the proportion of tramadol use among drug abusers declined sharply from 13.3% in 2009 to 3.4% in 2011 [8-11]. However, it is worth noting that tramadol abuse was still prevalent in some regions, and tramadol abuse shows a property of regional distribution. Among those, the percentage of tramadol use was highest in South China (5.1%), and tramadol popular use in Guangdong province was still relatively high [11]. According to statistics of Drug Monitoring Center of Guangdong Province, the number of tramadol abusers increases from 11 persons in 2004 to 4,492 persons in 2006 in Guangdong province [12]. Based on these reasons, all tramadol patients were recruited in Guangzhou city, Guangdong Province [12].

In recent years, many studies showed that, tramadol poisoning has become one of the most common causes of admissions to the emergency departments in Iran [5-9].

Although the issue of drug abuse is not a newcomer to the Egyptian society, tramadol has been associated with a wide range of drug abuse cases. Illegal drug transactions of tramadol had made it easily accessible and readily provided at cheap costs despite being a scheduled drug. The alleged usages of tramadol had also contributed greatly to its popularity and its massive use especially among Egyptian youth as a remedy for premature ejaculatory function and for extended orgasm and increase in sexual pleasure as promoted through many online drug stores and media [10,11].

Physical characters:

The molecular weight of tramadol hydrochloride is 299.84. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder[11].

Chemical structure

The molecular formula of tramadol hydrochloride is $C_{16}H_{13}NO_2$.HCl (Figure 1).

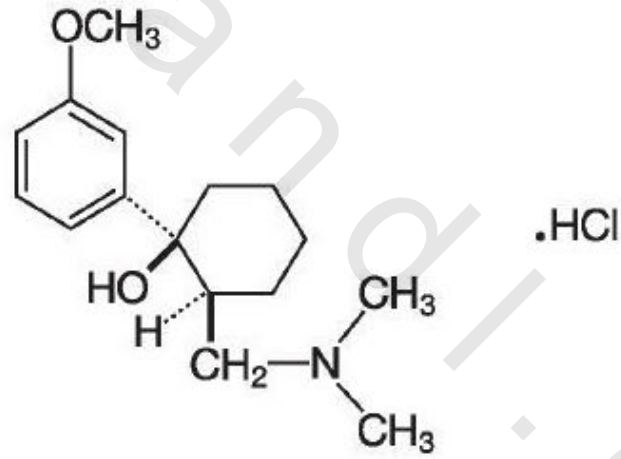

Figure (1): The molecular formula of tramadol hydrochloride [5].

The chemical name for tramadol hydrochloride is (±)cis-2-((dimethylamino) methyl)-1-(3-methoxyphenyl) cyclo-hexanol hydrochloride (Figure 2). It has two stereogenic centers at the cyclohexane ring. Thus, 2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexanol may exist in *four* different configurational forms:

(1*R*,2*R*)-isomer (1*S*,2*S*)-isomer
(1*R*,2*S*)-isomer (1*S*,2*R*)-isomer

The synthetic pathway leads to the racemate (1:1 mixture) of (1*R*,2*R*)-isomer and the (1*S*,2*S*)-isomer as the main products.[13] This racemate showed higher analgesic activity than either enantiomer in animals[14] and in humans [15].

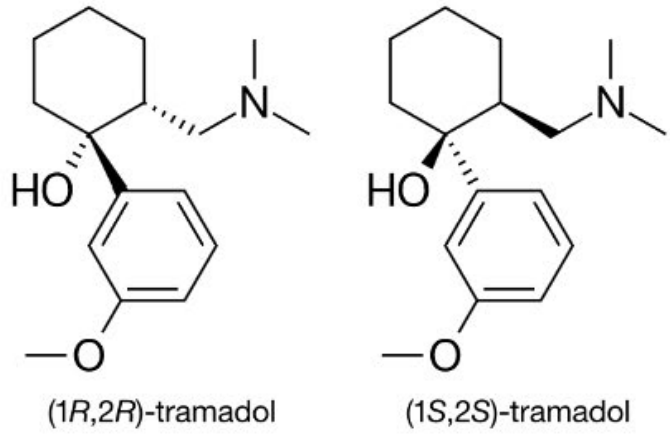

Figure (2): The chemical name for tramadol hydrochloride
(1*R*,2*R*)-*rel*-2-((Dimethylamino)methyl)-1(3methoxyphenyl)cyclohexanol[14]

Pharmacological characteristics

➢ **Pharmacodynamics**

Opioid activity is attributed to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite 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. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone as reported in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.[13]

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol.[14]

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids.[15]

➢ **Pharmacokinetics**

- **Absorption and bioavailability**

Tramadol is administered as a racemate and both the (-) and (+) forms of both tramadol and M1 are detected in the circulation. Tramadol hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tramadol hydrochloride tablets [16-19].

Peak plasma concentrations of tramadol hydrochloride occurs at two hours after administration in healthy adults. Steady-state plasma concentration of tramadol is achieved within two days with four times per day dosing. There is no evidence of self-induction[16-19].

- **Effects of food intake on absorbtion and bioavailability**

When tramadol hydrochloride was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol. However, peak plasma concentration or the extent of absorption of tramadol were not affected.[20]

- **Distribution**

The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 mcg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.[21-23]

- **Metabolism**

Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be N- and O- demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (O- desmethyltramadol) is pharmacologically active.[22,23]

Formation of M1 is dependent on CYP2D6 and thus, inhibition of this enzyme may affect the therapeutic response.[23] Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are "poor metabolizers" of several drugs, such as tricyclic antidepressants, and others. Based on a population Peak Concentration (PK) analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower. In vitro drug interaction studies in human liver microsomes indicates that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol by various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown.[23]

- **Elimination**

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5 to 6 and 7 hours. [22,23]

Mechanism of action

Tramadol acts by different mechanisms; as a μ-opioid receptor agonist, serotonin releasing agent, norepinephrine reuptake inhibitor, N-methyl-D-aspartate receptor (also known as the NMDA receptor or NMDAR) antagonist (IC_{50}=16.5 μM), 5-HT_{2C} receptor antagonist (EC_{50}=26 nM), $(\alpha 7)_5$ nicotinic acetylcholine receptor antagonist,[16] The transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor agonist, and M_1 and M_3 muscarinic acetylcholine receptor antagonist. TRPV1, also known as the capsaicin receptor and the vanilloid receptor 1, is a protein that, in humans, is encoded by the *TRPV1* gene. It was the first isolated member of the transient receptor potential vanilloid receptor proteins that in turn are a sub-family of the transient receptor potential protein group.[2,3] This protein is a member of the TRPV group of transient receptor potential family of ion channels.[4] The function of TRPV1 is detection and regulation of body temperature. In addition, TRPV1 provides sensation of scalding heat and pain (nociception). [24,25]

The analgesic action of tramadol is not fully understood, but it is believed to work through modulation of serotonin and norepinephrine in addition to its relatively weak μ-opioid receptor agonism. The contribution of non-opioid activity is demonstrated by the fact that the analgesic effect of tramadol is not fully antagonized by the μ-opioid receptor antagonist naloxone.[26]

Tramadol is marketed as a racemic mixture of the (1*R*,2*R*)- and (1*S*,2*S*)-enantiomers with a weak affinity for the μ-opioid receptor (approximately 1/6000th that of morphine. The (1*R*,2*R*)-(+)-enantiomer is approximately four times more potent than the (1*S*,2*S*)-(–)-enantiomer in terms of μ-opioid receptor affinity and 5-HT reuptake, whereas the (1*S*,2*S*)-(–)-enantiomer is responsible for noradrenaline reuptake effects. These actions appear to produce a synergistic analgesic effect, with (1*R*,2*R*)-(+)-tramadol exhibiting 10-fold higher analgesic activity than (1*S*,2*S*)-(–)-tramadol[26].

The serotonergic-modulating properties of tramadol give it the potential to interact with other serotonergic agents. There is an increased risk of serotonin toxicity when tramadol is taken in combination with serotonin reuptake inhibitors (e.g., SSRIs), since these agents not only potentiate the effect of 5-HT but also inhibit tramadol metabolism. Tramadol is also thought to have some N-Methyl-D-aspartate receptor (NMDA) antagonistic effects, which has given it a potential application in neuropathic pain states.[27]

Tramadol has inhibitory actions on the 5-HT_{2C} receptor. Antagonism of 5-HT_{2C} could be partially responsible for tramadol's reducing effect on depressive and obsessive-compulsive symptoms in patients with pain and co-morbid neurological illnesses.[5] 5-HT_{2C} blockade may also account for its lowering of the seizure threshold, as 5-HT_{2C} knockout mice display significantly increased vulnerability to epileptic seizures, sometimes resulting in spontaneous death. However, the reduction of seizure threshold could be attributed to tramadol's putative inhibition of GABA-A receptors at high doses.[26]

The overall analgesic profile of tramadol supports its use in the treatment of intermediate pain, especially chronic pain. It is slightly less effective for acute pain than hydrocodone, but more effective than codeine. It has a dosage ceiling similar to codeine, a risk of seizures when overdosed, and a relatively long half-life making its potential for misuse relatively low amongst intermediate strength analgesics. Tramadol has no clinically related effect on respiratory or cardiovascular parameters. Tramadol may demonstrate particularly useful in patients with poor cardiopulmonary function and in other special patient groups. [27]

Tramadol's primary active metabolite, *O*-desmethyltramadol, is a considerably more potent μ-opioid receptor agonist than tramadol itself. Thus, tramadol is in part a prodrug to *O*-desmethyltramadol. Similarly to tramadol, *O*-desmethyltramadol has also been shown to be a norepinephrine reuptake inhibitor, 5-HT_{2C} receptor antagonist, and M_1 and M_3 muscarinic acetylcholine receptor antagonist.[22]

Although there are many studies performed on thousands of volunteers to explore analgesics, Tramadol mechanism of action is not completely understood. From experimental studies, at least two complementary mechanisms seem to be valid: binding of parent and M1 metabolite to opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. The comparative contribution of both

Tramadol and M1 to human analgesia depends on the plasma concentrations of each compound. Apart from the analgesic effect, tramadol may cause a group of symptoms similar to that of an opioid. [26]

The different way in which tramadol provides analgesia with less side effects than the ones caused by other similar products may be explained by tramadol dual mechanism of action.

In animal and human models both opioid and monoaminergic mechanisms contribute to the analgesic efficacy of tramadol, with the monoaminergic mechanism likely accounting for more than half of the analgesic effect. [27]

In addition, it produces the beneficial effects that may reduce post-surgical pain, obstetric pain, cancer pain and chronic pain of mechanical and neurogenic origin. [24]

Since 2004, there has been a state of uncertainty and controversy about the use of nonsteroidal anti-inflamatory medications and cyclooxygenase (COX)-2 inhibitors, so other analgesics have started to be used for treating moderate to severe pain including tramadol.

Combined Tramadol analgesics: [27]

Because of its mechanism of action, Tramadol may be coadministered with other analgesics, especially those with peripheral action. Drug substances that depress CNS function may enhance the sedative effect of tramadol. [27]

Dose

Tramadol hydrochloride has been given in single oral doses of 50, 75 and 100 mg to patients with pain following surgical procedures and pain following oral surgery (extraction of impacted molars).[28,29]

In single-dose models of pain following oral surgery, pain relief was demonstrated in some patients at doses of 50 mg and 75 mg. A dose of 100 mg tramadol hydrochloride tended to provide analgesia superior to codeine sulfate 60 mg, but it was not as effective as the combination of aspirin 650 mg with codeine phosphate 60 mg.[28]

Tramadol hydrochloride has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving tramadol hydrochloride. Patients with a variety of chronic painful conditions were studied in double-blind trials of one to three months duration. Average daily doses of approximately 250 mg of tramadol hydrochloride in divided doses were generally comparable to five doses of acetaminophen 300 mg with codeine phosphate 30 mg (TYLENOL® with Codeine #3) daily, five doses of aspirin 325 mg with codeine phosphate 30 mg daily, or two to three doses of acetaminophen 500 mg with oxycodone hydrochloride 5 mg (TYLOX®) daily.[30,31,32]

In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day titration to a daily tramadol hydrochloride dose of 200 mg (50 mg four times per day), attained in 50 mg increments every 3 days, was found to result in fewer discontinuations due to dizziness or vertigo than titration over only 4 days or no titration.[32,33,34]

Contraindications

Tramadol hydrochloride tablets should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids. Tramadol hydrochloride tablets are contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol hydrochloride tablets may worsen central nervous system and respiratory depression in such patients.[35]

Warnings

Seizure Risk

Seizures have been reported in patients receiving tramadol hydrochloride within the recommended dosage range. Spontaneous postmarketing reports indicate that seizure risk is increased with doses of tramadol hydrochloride above the recommended range. Concomitant use of tramadol hydrochloride increases the seizure risk in patients taking:[36,37,38]

- Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or
- Other opioids.

Administration of tramadol hydrochloride may enhance the seizure risk in patients taking:

- MAO inhibitors,
- Neuroleptics, or
- Other drugs that reduce the seizure threshold.

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol hydrochloride overdose, naloxone administration may increase the risk of seizure.[39,40]

Suicide Risk

- Tramadol hydrochloride should not prescribed for patients who are suicidal or addiction-prone.
- Tramadol hydrochloride tablets should be prescribed with caution for patients who are taking tranquilizers or antidepressant drug and patients who use alcohol in excess and who suffer from emotional disturbance or depression.[41]

The legal prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics.[42,43,44]

Tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs[41].

Serotonin Syndrome Risk

The development of a potentially life-threatening serotonin syndrome may occur with the use of tramadol products, including tramadol hydrochloride, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs, and triptans, with drugs which impair metabolism of serotonin (including MAOIs), and with drugs which impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors). This may occur even within the recommended dose.[45,46]

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).[47]

Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol hydrochloride. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive tramadol hydrochloride.[48]

Respiratory Depression

Tramadol hydrochloride should be given with caution in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol hydrochloride are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.[46,47]

Interaction with Central Nervous System (CNS) Depressants

Tramadol hydrochloride should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol hydrochloride increases the risk of CNS and respiratory depression in these patients.[48]

Interactions with Alcohol and Drugs of Abuse

Tramadol may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.[49]

Increased Intracranial Pressure or Head Trauma

Tramadol hydrochloride should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and

may be markedly exaggerated in such patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving tramadol hydrochloride.[50]

Use in Ambulatory Patients

Tramadol hydrochloride may impair the mental and physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.[51]

Use with MAO Inhibitors and Serotonin Reuptake Inhibitors

Use tramadol hydrochloride with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of tramadol hydrochloride with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.[52]

Misuse, Abuse, and Diversion

Tramadol has μ-opioid agonist activity. Tramadol hydrochloride can be sought by drug abusers and people with addiction disorders and may be subject to criminal diversion. [53]

The possibility of illegal or illicit use should be considered when prescribing or dispensing tramadol hydrochloride in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Misuse or abuse poses a significant risk to the abuser that could result in overdose and death .[53]

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.[54]

Risk of Overdosage

Patients taking tramadol should be warned not to exceed the dose recommended by their physician. Tramadol products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a cause of drug-related deaths. Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS additive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS depressant drugs. Patients should be advised of the additive depressant effects of these combinations.[54]

Serious potential consequences of overdosage with tramadol hydrochloride tablets are central nervous system depression, respiratory depression and death. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment.[55]

Withdrawal

Withdrawal symptoms may occur if tramadol hydrochloride is discontinued abruptly. Reported symptoms have included anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been reported less frequently with tramadol hydrochloride discontinuation include panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be avoided by tapering tramadol hydrochloride at the time of discontinuation.[56]

Precautions

Acute Abdominal Conditions

The administration of tramadol hydrochloride may complicate the clinical assessment of patients with acute abdominal conditions.[55]

Use in Renal and Hepatic Disease

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, dosing reduction is recommended. Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. In cirrhotic patients, dosing reduction is recommended.[56]

With the prolonged half-life in these conditions, achievement of steady-state is delayed, so that it may take several days for elevated plasma concentrations to develop.[56]

Table(1): Cumulative Incidence of Adverse Reactions for Tramadol Hydrochloride in Chronic Trials of Nonmalignant Pain (N=427)[55,56]

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/Vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
"CNS Stimulation"1	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

"CNS Stimulation" is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations

Incidence 1% to less than 5% is possibly causally related . The following lists adverse reactions that occurred with an incidence of 1% to less than 5% in clinical trials, and for which the possibility of a causal relationship with tramadol hydrochloride exists.

Drug interactions

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. In a previous experimental study, tramadol was shown to be a mild inducer of selected drug metabolism pathways.[26]

- **Drug interaction with carbamazepine**

Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol, as carbamazepine increases tramadol metabolism. Due to the seizure risk associated with tramadol, concomitant administration of tramadol hydrochloride and acetaminophen with carbamazepine is not recommended.[26]

- **Drug interaction with quinidine**

Tramadol is metabolized to M1 by CYP2D6. Quinidine is a selective inhibitor of that isoenzyme; so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. In vitro drug interaction studies in human liver microsomes showed that tramadol had no effect on quinidine metabolism. [26]

- **Drug interaction with inhibitors of CYP2D6**

In vitro drug interaction studies in human liver microsomes indicate that concomitant administration of tramadol with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol. [26]

- **Drug interaction with MAO Inhibitors**

Interactions with MAO Inhibitors, due to interference with detoxification mechanisms, have been reported for some centrally acting drugs. Concomitant use of serotonin re-uptake inhbitors and MAO inhibitors may enhance the risk of adverse events, including seizure and serotonin syndrome.

- **Drug interaction with warfarin like compounds**

Post-marketing surveillance of both tramadol and acetaminophen individual products have revealed rare alterations of warfarin effect, including elevation of prothrombin times. While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when tramadol hydrochloride and acetaminophen and warfarin-like compounds are administered concurrently.[26,55]

- **Drug interaction with digoxin**

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.

Efficacy of tramadol as a painkiller

Tramadol has a dose-dependent effect that lies between that of codeine and morphine, with a parenteral potency comparable to that of pethidine, i.e. about 10-20% of the gold standard morphine.[2] Oral bioavailability is high (85-100%) and permits easy conversion from the oral to the parenteral route and visa versa. Surprisingly, the efficacy of tramadol is not associated with the usual serious opioid side effects which can often be dose-limiting. Furthermore, unlike non steroidal anti-inflammatory drugs, tramadol has no serious adverse gastrointestinal effects, such as gastrointestinal bleeding. Numerous clinical trials have proven its efficacy and safety over a broad range of painful conditions, both acute and chronic; however, in severe pain morphine may be superior to tramadol.[3] It is this combination of safety with good efficacy that has made tramadol a unique addition to the analgesic.[25-29]

Although several studies have addressed the antinociceptive effect of tramadol for treatment of postoperative pain, its pre-emptive analgesic effect in the treatment of postsurgical pain is not clear.[32,33] Pre-emptive analgesia is defined as `analgesic intervention provided before surgery to prevent or reduce subsequent pain'.[34]

This effect has been demonstrated in animal experiments but, while some clinical results have supported the concept, others have failed to show any effect.[34] Two reports suggest that postoperative morphine consumption is reduced when morphine is given at the start of surgery rather than at the end.[35,36]

Advantages of tramadol over other opioid preparations

1. Respiratory depression

Respiratory depression is less pronounced, and occurs less often, in comparison to equianalgesic doses of morphine.[57,58] In large clinical and post-marketing studies including over 21,000 patients, no clinically relevant respiratory depression was reported.[59-63] However, respiratory depression can occur, in particular with overdose[8] (as described in children[64,65]) or with impaired renal function,[66] possibly due to retention of the active metabolite M1.

2. Constipation:

Another opioid side effect, which is reduced with tramadol use, is constipation.[66] Clinically, this has proven to be a significant advantage with long-term therapy, but could also be beneficial in the prevention of ileus postoperatively.[66]

3. Dependence potential

The effects of long-term opioid intake on the development of tolerance, physical dependence and psychological addiction are reduced with tramadol use. In an experimental study, it was demonstrated that even experienced opioid users could not recognize tramadol in lower doses as an opioid,[67] whereas in higher doses they could recognize it, but did not "like" it, presumably due to its tricyclic-like properties. Hence, the incidence of abuse of tramadol is low in all post-marketing surveys. The FDA reports a rate of abuse in the range of 1 in 100,000 patient exposures.[68] Rare cases of withdrawal reactions after abrupt discontinuation of tramadol have also been reported.[62,67]

Precautions for tramadol use

1. In epileptics and patients on tricyclies, SSRIs, high dose opiods

It has been reported that 15% to 35% of hospital referred patients with tramadol poisoning experience seizures [5-7]. The lowest dose associated with seizures was 200 mg in one study [5] and 300 mg in another[9].

Seizures, CNS depression, and loss of protective airway reflexes are serious risk factors for pulmonary aspiration. Moreover, most seizures due to tramadol poisoning occur within the first 6 h of ingestion, with some studies reporting onset of seizures within the first 2 h[6].

There is an increasing belief in tramadol-induced seizures. Overall, there is no good evidence that tramadol use by itself can induce idiopathic seizures, except possibly in excessive doses.[15] When seizures do occur with tramadol use, they are commonly of short duration and are easily treatable. In one reported case of seizures, the convulsions were induced by naloxone administration.[35] However, tramadol should be used with caution in patients with a history of epilepsy and those on concomitant seizure threshold-lowering medication (e.g. tricyclics, selective serotonin re-uptake inhibitors, high dose opioids).[35]

2. In patients on monoamine oxidase inhibitors (MAOIs)

Some cases were recorded to induce serotonin syndrome by combination of tramadol with SSRIs.[43,44] Such combinations may be used with caution. Although no reports of drug interactions with MAO inhibitors have been published, the concomitant use of MAOIs with tramadol is contraindicated as a safety precaution. [45]

Tramadol overdose

Signs and symptoms of adverse effects of tramadol overdose

Adverse effects of tramadol overdose are classified into groups according to their incidence rate (Figure 3).[1,15-20]

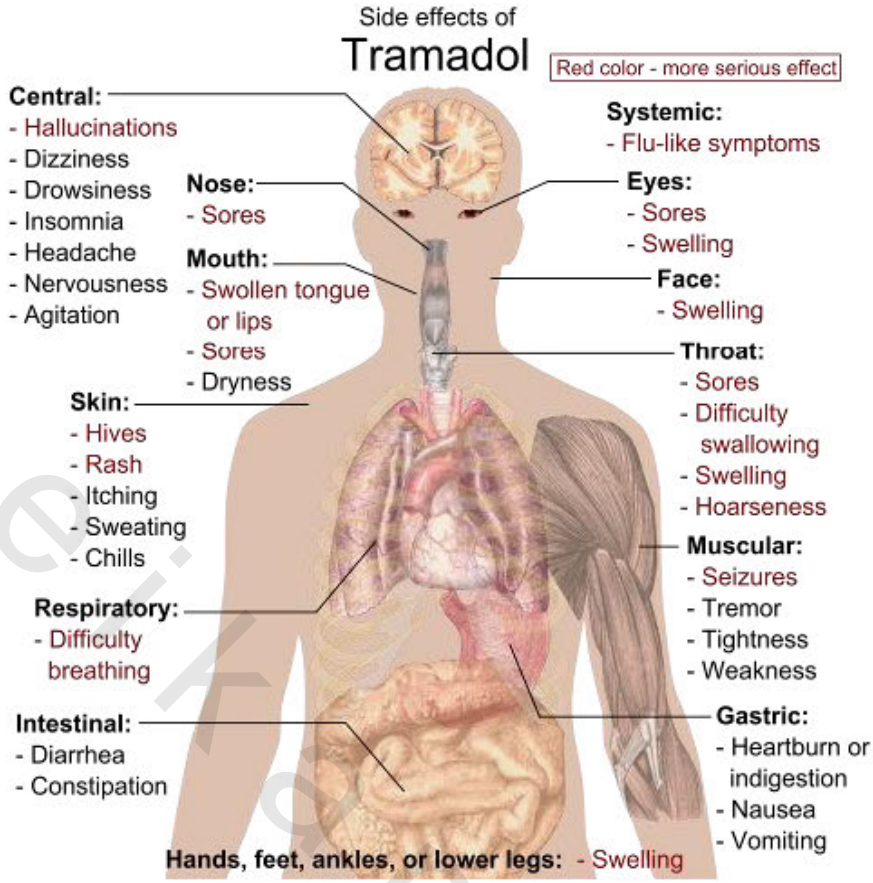

Figure (3): Main side effects of tramadol. Red color denotes more serious effects, requiring immediate contact with health provider.[14]

- Cardiovascular: vasodilation, syncope, orthostatic hypotension, tachycardia, hypertension, myocardial ischaemia and palpitation.
- Respiratory: respiratory depression, pulmonary oedema and pulmonary embolism,
- Central nervous system: anxiety, confusion, coma, dizziness, headache, agitation, seizures, vertigo, epileptiform convulsions, somnolence, nervousness, visual disturnbance, miosis, hypertonia, spasticity, paraesthesia, involuntary muscle contractions, blurred vision, migraine, coordination disturbance, euphoria, hallucinations, tremor, amnesia, tinnitus, difficulty in concentration, speech disorders, abnormal gait, sleep disorders and suicidal tendency.[20]
- Gastrointestinal: nausea, vomiting, constipation, abdominal pain, dyspepsia, flatulence, anorexia and weight loss, dry mouth, hepatitis, liver failure, stomatitis and gastrointestinal bleeding,
- Genitourinary: dysuria, urinary retention, urinary frequency, renal failure, menopausal symptoms and menstrual disorder.
- Dermatologic: rash, pruritus (itchiness), sweating, urticaria (hives), hypothermia, allergic reactions and angioneurotic oedema and Stevens-Johnson syndrome/ toxic epidermal necrolysis (potentially fatal skin reactions).
- Miscellaneous: anaphylaxis, malaise, fatigue, asthenia and anemia.[23]

The most common adverse events reported in clinical trials and post-marketing studies were, in decreasing order of frequency (range from 7 to 1%): nausea, dizziness, drowsiness, tiredness, fatigue, sweating, vomiting, dry mouth and postural hypotension. Nausea, a well-documented opioid side effect, seems to occur with an incidence comparable to that in other opioids, while vomiting is less common. The incidence of nausea varied with route and setting of administration from 3% in controlled trials of oral medication, to 21% with IV use via patient controlled analgesia (PCA) pumps in the postoperative period. Avoidance of early mobilization after IV administration, initiation of oral treatment at low doses with gradual increase, and use of antiemetics (phenothiazines and/or 5-HT_3-antagonists) can reduce the incidence and severity of this side effect.[41]

Sweating is a side effect specific to tramadol, due to its monoaminergic effects, and it can be quite distressing to a small number of patients. In rare situations, sweating may be severe enough to necessitate discontinuation. [41]

Effect of Long term use of tramadol

There are suggestions that chronic opioid administration may induce a state of immune tolerance,[21] although tramadol, in contrast to typical opioids may enhance immune function.[22-25]

I. Physical dependence and withdrawal

Long-term use of high doses of tramadol may be associated with physical dependence and a withdrawal syndrome.[26] Tramadol causes typical opiate-like withdrawal symptoms as well as atypical withdrawal symptoms including seizures. The atypical withdrawal symptoms are probably related to tramadol's effect on serotonin and norepinephrine re-uptake. Symptoms may include anxiety, depression, anguish, severe mood swings, aggressiveness, brain "zaps", electric-shock-like sensations throughout the body, paresthesias, sweating, palpitations, restless legs syndrome, sneezing, insomnia, vivid dreams or nightmares, tremors, and headache. In most cases, tramadol withdrawal will set in 12–20 hours after the last dose, but this can vary. Tramadol withdrawal manifestation last longer than that of other opioids; seven days or even more of acute withdrawal symptoms can occur as opposed to typically three or four days for other codeine analogues.[27-30]

II. Psychological dependence and recreational use

Tramadol is generally considered to be safe and thought to have minimal potential for abuse. Despite a range of studies, still no consensus data exist on the dependence potential of tramadol. Studies from animal experiment hold controversial finding, one is that tramadol was not likely to induce tolerance and physical dependence in mice [13] and the other is that conditioned place preference (CPP) in rats was produced[14, 15]. Though tolerance and dependence were not described after repeated administration of tramadol in human[16,17], case reports that tramadol can lead to dependence continue to emerge[18,19]. It was suggested that the abuse liability of tramadol may be greater than what assumed by hitherto [20].

Furthermore, Grünenthal has promoted it as having a lower risk of opioid dependence than traditional opioids, claiming little evidence of such dependence in clinical trials however, Grünenthal never claimed it to be non-addictive. They offer the theory that, since the M1 metabolite is the principal agonist at μ-opioid receptors, the

delayed agonist activity reduces the abuse liability. The norepinephrine reuptake inhibitor effects may also play a role in reducing dependence potential.[20]

In rare cases, dependence may occur after as little as three months of use at the maximum dose generally depicted at 400 mg per day. However, both physicians and health authorities generally consider dependence liability is relatively low. [20]

Because of the possibility of convulsions at high doses for some users, recreational use can be very dangerous.[33] Tramadol can cause a higher incidence of nausea, dizziness, loss of appetite compared with opiates, which could deter abuse.[34] Compared to hydrocodone, fewer patients choose to abuse tramadol.[35] It may also have a large effect on sleeping patterns and high doses may cause insomnia. Though there is no scientific proof, tramadol lessens effects of opiates or is a mixed agonist-antagonist, some people especially those on methadone, both for maintenance and recreation get the impression it is, while someone else might benefit being prescribed both for pain and breakthrough pain.[36]

Management of Tramadol overdose:
Laboratory investigations

Tramadol and *O*-desmethyltramadol may be quantified in blood, plasma or serum to monitor for abuse, confirm a diagnosis of poisoning or assist in the forensic investigation of a traffic or other criminal violation or a sudden death. Most commercial opiate immunoassay screening tests do not cross-react significantly with tramadol or its major metabolites, so chromatographic techniques must be used to detect and quantitate these substances. The concentrations of *O*-desmethyltramadol in the blood or plasma of a person who has taken tramadol are generally 10–20% those of the parent drug.[74,75,76]

Morteza, et al., (2012) [77] explored the tramadol intoxication clinical signs and symptoms and laboratory data, they found that, the average dose of tramadol had been ingested was 745.87±453.05 mg. Among laboratory abnormalities, the most common findings were prolonged PT (18.3%) and increased ALT (5.6%).

Treatment of Tramadol overdose[78,79]

1. Hospitalization is mandatory.
2. Observe patient for recurrence of CNS and respiratory depression.
3. Establish clear airway, adequate ventilation and oxygenation.
4. Assisted ventilation with positive end expiratory pressure may be necessary if pulmonary oedema is a complication.
5. Care for circulation.
6. Empty the stomach: give a dose of activated charcoal if presentation is within 1-2 hours of ingestion. Gastric aspiration or lavage may indicated if presentation is soon after ingestion in patients known to have taken large quantities.[78]
7. Narcotic antagonists as an antidotes:
    - Pure narcotic antagonist:
        - ❖ Naloxone (Narcan) I.V: it is the antidote of choice (1-2 mg for adult and 0.01 mg/kg body weight for children) if coma or respiratory depression are present, repeat the dose if there is no response after 2 minutes. The plasma half life of naloxone is shorter than that of most opioids and therefore necessary where

repeated dose have been required. It can be used as both a diagnostic and therapeutic agent.
- ❖ Nalmefene: it has a larger duration of action than naloxone.
- ❖ Naltrexone.

- Mixed narcotic agonist-antagonist: not used nowadays.

8. To treat seizures, administration of I.V. diazepam bolus (dose: 5-10 mg initially which may be repeated every 15 minutes. Up to 30 mg. Child: 0.25-0.4 mg/kg/dose up to 10 mg/dose.
9. Tramadol is minimally eliminated from the serum by haemodialysis.
10. I.V. fluids and laxative.
11. Follow up is important.

The efficacy of oral activated charcoal (AC) for the adsorption of drugs and poisons has been widely described in the literature [78]. AC can prevent systemic absorption of drugs if administrated within 1–2 hours of ingestion and possibly longer after ingestion of sustained-release preparations or drugs that delay gastric emptying, such as opioids or antimuscarinic drugs. Since routine use of AC is discouraged[78], it is important to consider the risks and benefits of AC on a drug-by-drug basis.

Many patients vomit while some aspirate gastric contents into the lungs, causing pneumonitis[2-4]. Significant predictive factors for aspiration pneumonitis after drug overdose include a Glasgow Coma Scale score of <15, emesis, seizure, and ingestion of tricyclic antidepressants[79]. The mortality for patients with aspiration pneumonitis has been reported to be 8.5% compared with 0.4% for those without aspiration pneumonitis, with patients with aspiration pneumonia having a significantly longer hospitalization[79].

Important complications of tramadol poisoning include seizures as well as depression of the central nervous system (CNS) and respiratory system[79].

Seizure onset may occur early after tramadol ingestion, making pulmonary aspiration of gastric contents and AC more likely. It is believed that this treatment should be avoided unless the patient is already intubated with an endotracheal tube. Moreover, the risk and benefit of administration of AC should be considered in these patients to avoid potential aspiration pneumonitis unless the patient is already intubated and the airways are secured.[79]

As one possible method for reducing drug-related deaths caused by opioid overdose, two significant adverse reactions which known to potentially occur with tramadol - seizures and serotonin syndrome- could dramatically be controlled by naloxone. Therefore, most guidelines for treatment of opioid overdose recommend short-acting opioid antagonist naloxone as the first step of treatment after supportive care [80]. Naloxone, is a phenanthrene compound structurally related to morphine. It was the first opiate receptor antagonist introduced in clinical practice [80,81] and has been widely used to antagonize the effects of opiate drugs. Indeed, most of biological effects of the analgesics have been long classified as opiate or non-opiate depending on whether or not they were reversed by naloxone[81].

Despite all advantages of naloxone, recent data showed serious adverse effects including several instances of seizures following naloxone administration [82]. Although the seizurogenic effects of low-dose naloxone in tramadol overdose has been reported as rare it could increase the mortality in patient who is in the risk of seizure. Esmaeil, et al., (2012)[81] found that, naloxone induced a seizurogenic effect in patients with tramadol overdose. This finding could be considered in the management of patients with tramadol overdose.

Regulations for Tramadol use

Tramadol is classified as a Schedule 4 in the US, Schedule 5 in Australia and has been rescheduled in Sweden rather than as a Schedule 8 Controlled Drug like opioids.[31] Similarly, unlike opioid analgesics, tramadol is not currently scheduled as a controlled substance by the U.S. Drug Enforcement Administration. However, it is controlled in certain states. Nevertheless, the prescribing information for Ultram warns that tramadol "may induce psychological and physical dependence of the morphine-type".[32]

In May 2009, the United States Food and Drug Administration issued a Warning Letter to Johnson & Johnson, alleging that a promotional website commissioned by the manufacturer had "overstated the efficacy" of the drug and "minimized the serious risks." The company which produced it, the German pharmaceutical company Grünenthal GmbH, were alleged to be guilty of "minimizing" the habituating nature of the drug, although it showed little abuse liability in preliminary tests. [13] The 2010 Physicians' Desk Reference contains several warnings from the manufacturer, which were not present in prior years. The warnings include stronger attention regarding the habituating potential of tramadol, the possibility of difficult breathing while on the medication, a new list of more serious side effects, and a notice that tramadol is not to be used in place of opiate medications for addicts. Tramadol is also not to be used in efforts to wean addict patients from opiate drugs, nor to be used to manage long-term opiate addiction.[29]