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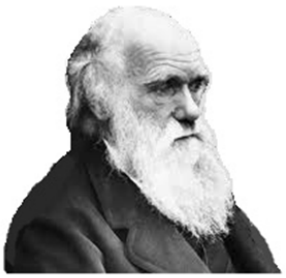

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Tramadol and its health implications

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ABSTRACT

Tramadol is classified as a pain reliever having analgesic properties. Pain is an unpleasant sensation that occurs most commonly as a result of tissue injury. Most opioid medicines are classed as alkaloid compounds and are classified as narcotics because they work on the central nervous system (CNS) to treat pain in conditions such as osteoarthritis, cancer, tooth pain, and kidney discomfort. Tramadol is plentiful in the roots of *Nauclea latofolia*. It can be chemically and biosynthetically produced from cyclohexanone and L-phenylalanine, respectively. The tramadol dose determines the toxicity stage. The medicine can be detoxified in the liver using monooxygenase enzymes and conjugating agents if taken in excess of the recommended dose. Tramadol works on the central nervous system by acting as a vulnerable agonist and inhibiting serotonin re-uptake. Seizures, genitourinary, dermatologic, and respiratory depression are just a few of tramadol's many side effects. The focus of this research will be on tramadol and its health consequences.

***Keywords*:** Tramadol, Narcotic, Pain, Opioid

1. INTRODUCTION

Tramadol

Tissue injury frequently results in unpleasant pain, which is impacted by behavior and community variables and is accountable for psychological and emotional distress. It is divided into three categories: Nociceptive aching I (produced via tissue injury) Neuropathic pain (ii) (duetonerveinjury) (iii) Neuroplastic pain (as a result of musculoskeletal illness, such as

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inflammatory pain) (Kidd et al., 2007). Various pharmacological treatments, such as paracetamol, NSAID class medicines, antidepressants, anti-cytokines, and opioids, have been utilized to treat it using tablets. Tramadol is a pain reliever that has exceptional analgesic properties (Dayer *et al.*, 2007; Bravo *et al.*, 2017).

Opioid medications belong to the alkaloid class of substances derived from "*Papaver somniferum* L.," and are classified as narcotics since they act on the central nervous system to relieve pain (Martinez *et al.*, 2016). Opioid abuse and addiction cause major health consequences (Karbakhsh *et al.*, 2007; Zaaijer *et al.*, 2004). Opioid analgesics work by attaching to opioid receptors found in the brain, spinal cord, and other regions of the body, reducing pain experience.

Afghanistan is responsible for the world's largest opium poppy cultivation (Rosen *et al.*, 2004); opioid medicines such as morphine, codeine, fentanyl, hydrocodone, meperidine, methadone, and oxycodone act by interacting with the primary target known as the opioid receptor (MOR). In the early stages of opioid withdrawal, tramadol is widely used to help users manage their symptoms (Threlkeld *et al.*, 2006).

Tramadol is a hydrochloride of 2-(dimethylamino)-methyl)-1-(3-methoxyphenyl) cyclohexanol. It's a four-phenyl-piperidine derivative of the opioid codeine. It was developed and synthesized for the first time in 1962 by a German business (Grunenthal GmbH) for the treatment of pain, and it was first sold in 1977 under the brand name 'Tramadol.' It became available in the United States after 1995. (Patterson *et al.*, 2017). It's now known as ULTRAM, and it's a racemic mixture of (R, R)- and (S, S)-enantiomers that's generally available as a hydrochloride salt (WHO, 2013). Morphine, for example, is a very powerful analgesic, although it is used less frequently due to its side effects of respiratory depression, addiction, dependency, and constipation.

Tramadol's analgesic potency is ten times lower than morphine's, but it is chosen since it is safer. When compared to other opioid analgesics, tramadol is considered safe because it does not produce respiratory depression or addiction (Kenzie *et al.*, 2001). Furthermore, tramadol has a lower potential for abuse when delivered by parenteral method. It acts as an analgesic by agonistically activating MOR, central GABA catecholamine, and serotonergic receptors. It also has antitussive properties due to its ability to bind to receptors (Hennies *et al.*, 2008).

Sources of Tramadol

Natural source

Because the natural origin of tramadol is still a topic of controversy, the biosynthesis of tramadol is a hypothetical process. Boumendjel *et al.*, (2013) on the other hand, recently discovered tramadol in *Nauclea latofolia L*. Tramadol is detected in the roots and bark of Nauclea latofolia (0.00002 percent w/w) (Kusari *et al.*, 2014). Tramadol was extracted and characterized using high-performance liquid chromatography (HPLC) (Fig. 1), and its analgesic properties were investigated in a mouse model in an in vivo study.

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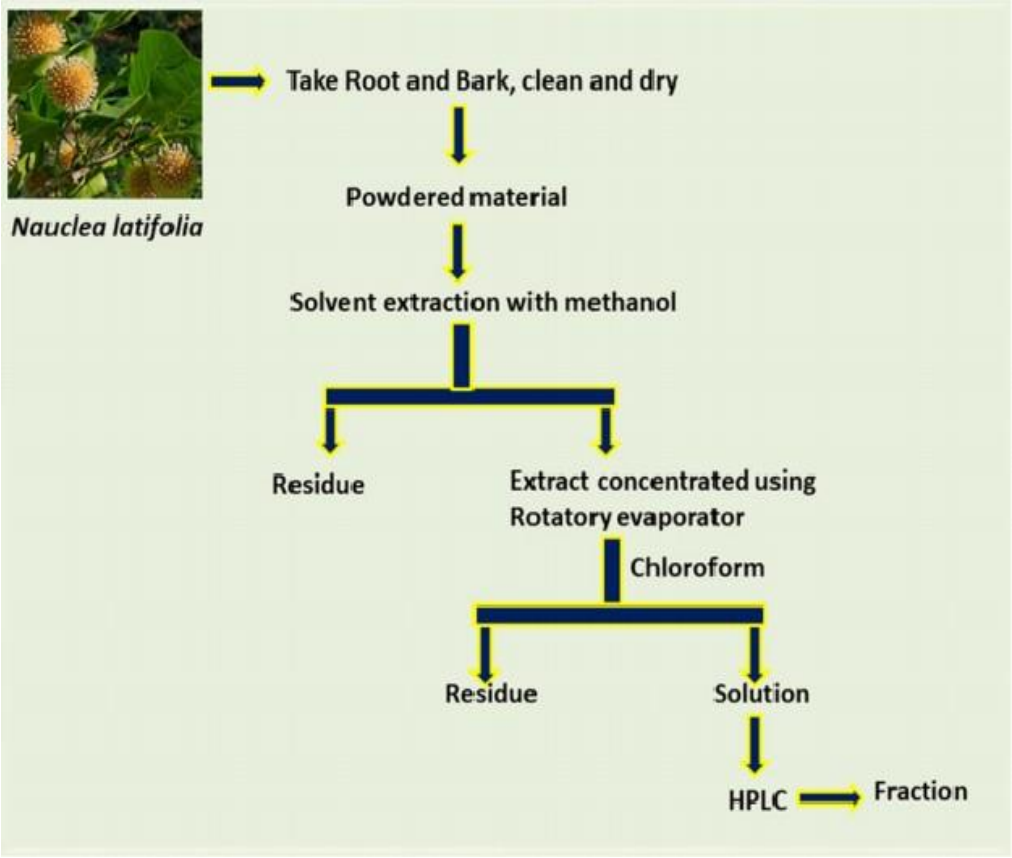

Figure 1. Extraction process of Tramadol (Kusari *et al.*, 2014)

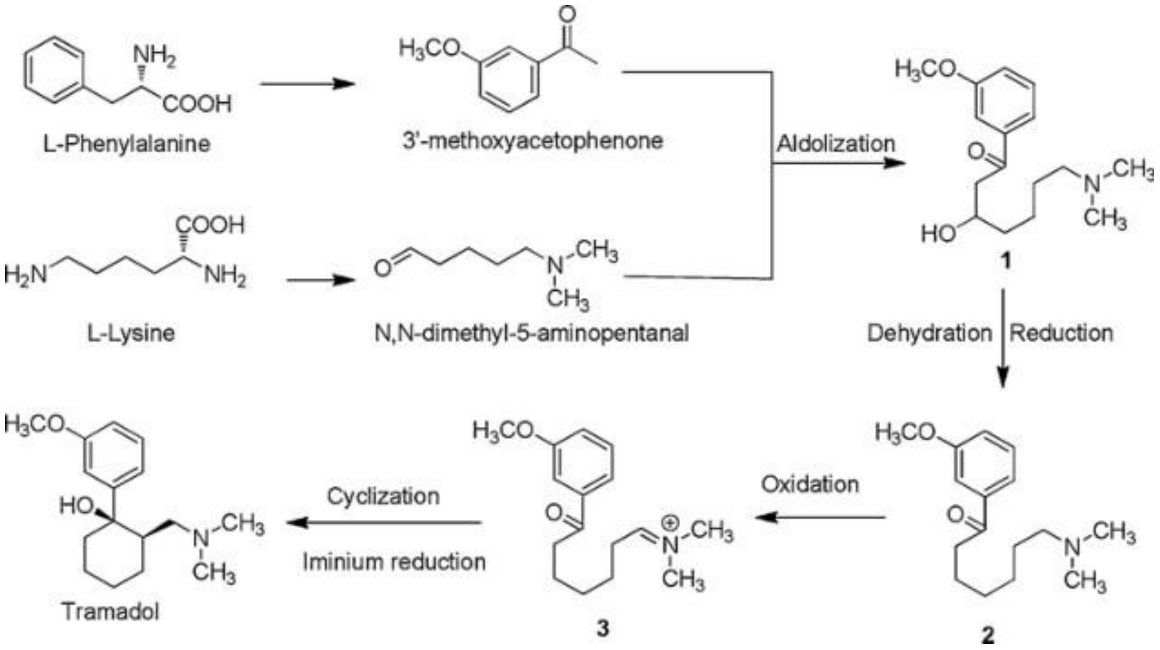

Figure 2. Biosynthesis of tramadol (Lecert-Schmidt *et al.*, 2015)

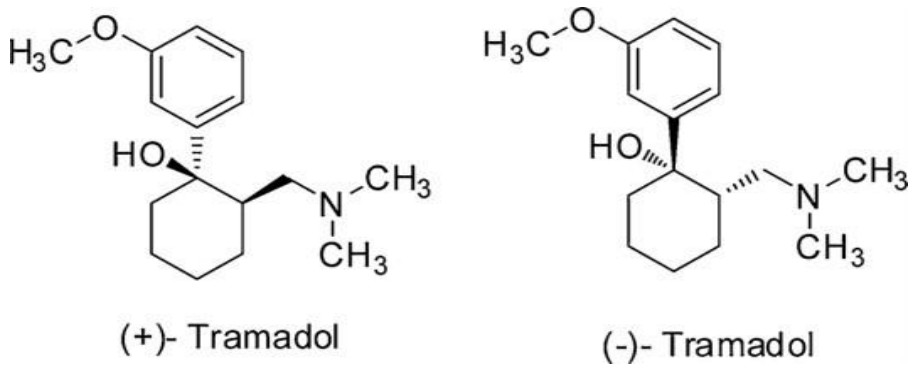

Figure 3. Structure of isomer of Tramadol HCl (Grond *et al.*, 2004)

History of Tramadol

In 1992, during the Committee's 28th meeting, tramadol was pre-reviewed for the first time. Because of its minimal abuse liability, as evidenced by human research on its subjective effects and the lack of serious abuse, the Committee did not suggest critical evaluation. Tramadol was pre-reviewed again at the 32nd conference in 2000. The Committee noticed a high number of cases of withdrawal syndrome and dependence recorded as adverse drug responses, as well as its potential to cause morphine-type dependence, and suggested that tramadol be subjected to a thorough evaluation. The Committee agreed at its 33rd meeting in 2002 that the material was insufficient to support international tramadol regulation, but that it was sufficient to recommend that WHO maintain the medication under monitoring. Tramadol was subsequently pre-reviewed at the 34th meeting in 2006. The Committee determined that there was insufficient evidence to justify a critical assessment because tramadol continued to exhibit a low degree of misuse despite a significant increase in the amount of its therapeutic usage (WHO, 2014).

Chemistry of Tramadol

Tramadol is a codeine analogue made from 4-phenylpiperidine(2-(dimethyl aminomethyl)-1-(3-methoxyphenyl) cyclohexanol). Tramadol in its commercial form is a mixture of the dextro (+) and levo (-) enantiomers (Fig. 3). Water and ethanol are both active solvents for tramadol hydrochloride. Tramadol's di-methyl aminomethyl group methylates the ring nitrogen of codeine and morphine, which is required for binding to MOR. It is metabolized through nitrogen demethylation, oxygen, and conjugation processes (Grond *et al.*, 2004). Tramadol has a molecular weight of 263.19, a hydrogen bond donor of 1, a hydrogen bond acceptor of 2, a molar refractivity of 1.55, and a partition coefficient of 2.88, according to the Lipinski rule of five.

Chemical Synthesis of Tramadol

The chemical synthesis of tramadol is simple and cost-effective; the chemical synthetic pathway is depicted in Figure 2. Cyclohexanone is utilized as a starting material, and compounds 2 and 3 are made by reacting it with dimethylamine hydrochloride and n-methyl-1-

phenylmethanamide. In the presence of ethyl ether and HCl, these chemicals 2 and 3 react with (3-methoxyphenyl) lithium to generate Tramadol (Jarvi *et al.*, 2002; Poupon *et al.*, 2011).

The major products of the synthetic process are the racemate (1:1 mixture) of (1R, 2R)-isomer and the (1S, 2S)-isomer. There were also minor amounts of the racemic mixture of the (1R, 2S)-isomer and the (1S,2 R)-isomerare. Recrystallization of the hydrochlorides allows the isolation of the (1R, 2R)-isomer and the (1S, 2S)-isomer from the diastereomeric minor racemate [(1 R, 2 S)-isomer and (1S, 2R)-isomer]. The substance tramadol is a racemate of the (1R, 2R)- (+) - and (1S, 2S)- () - enantiomers' hydrochlorides. (R)- () - or (S)- (+) - mandelic acid were used to characterize the resolution of the racemate [(1R, 2R)- (+)- isomer / (1S, 2S)- ()-isomer] (Zynovy *et al.*, 2000).

Despite established physiological differences (Burke et al., 2002) between the (1R, 2R)- and (1S, 2S)-isomers, tramadol is utilized as aracemate, because the racemate exhibited better analgesic effectiveness than either enantiomer in animals (Raffa *et al.*, 2003) and humans (Grond *et al.*, 2005).

Clinical Uses of Tramadol

Table 1. Uses of Tramadol in different Types of Pain

Type of pain	Uses	References
Osteoarthritis	It is used as intermediate components	Cepeda *et al.*, 2007
Dental	For pain treatment in canal (root)	Malik *et al.*, 2015
Cancer	Aids to relieve pain in cancer patients	WHO, 2013
Heart pain	It used as beta blockers and nitrates	Sunshine *et al*, 2004
Postoperative	To reduce pain after surgery	Yilmaz *et al.*, 2015
Renal pain	To reduce pain in ureteral calculi	Hussein *et al.*, 2015

Acute pain

Tramadol has been thoroughly studied in cardiothoracic (James *et al.*, 2006; Lomona *et al.*, 2005), orthopaedic (Kuper *et al.*, 2005; Hupkins *et al.*, 2008), general (Rud *et al.*, 2004; Canepa *et al.*, 2003), and paediatric surgery (Barsoum *et al.*, 2005; Bosenberg *et al.*, 2008). Tramadol compares favorably to a variety of analgesics in the acute setting, from paracetamol to morphine, in terms of efficacy and adverse event occurrence. Oral tramadol as an analgesic has been shown to be effective (McQuay *et al.*, 2008). Tramadol is generally more effective than oral analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), pentazocine, dextropropoxyphene, and combination formulations containing paracetamol, though single-dose oral dextropropoxyphene 65 mg plus paracetamol 650 mg was found to have similar analgesic efficacy to tramadol 100 mg in comparative studies (Lehmann *et al.*, 2007; Sunhine *et al.*, 2002). Parenteral administration has mostly been linked to the treatment of postoperative

pain. Tramadol doses ranging from 50 to 400 mg are given intravenously and induce analgesia (Bamigbade *et al.*, 2008; Duthie *et al.*, 2008). Tramadol has been demonstrated to be equally effective as morphine for postoperative pain management following abdominal surgery (Vickers *et al.*, 2005). Tramadol and morphine infusions 48 hours after abdominal hysterectomy had equivalent analgesic effectiveness (Wilder-Smith *et al.*, 2009). During the infusions, there was nosomatic or visceral sensitization. Tramadol 1 mg/kg IV has been used to treat postoperative shivering with effectiveness (De-Witte *et al.*, 2007). During regional anaesthesia for caesarean delivery, intravenous tramadol 0.25 mg/kg and 0.5 mg/kg is beneficial in managing intraoperative shivering (Chan *et al.*, 2009).

Chronic pain

Tramadol has been demonstrated to be useful in the treatment of chronic pain in a variety of situations, as one may expect given its analgesic action modes (Budd *et al.*, 2009). Chronic pancreatitis (Bamigbade *et al.*, 2008), neuropathic pain (diabetic peripheral neuropathy, postherpetic neuralgia) (Mackin *et al.*, 2007; Harati *et al.*, 2008), and rheumatology (osteoarthritis, fibromyalgia) are examples of these conditions (Roth *et al.*, 2008; Biasi *et al.*, 2008). Tramadol works well in a variety of ways (both orally and intra-articularly) (Budd *et al.*, 2009). Tramadol reduces acute and chronic inflammation in rats without changing immunological systems (Bianchi *et al.*, 2009). In the treatment of osteoarthritis of the ankle, knee, and hip joints, intraarticular tramadol of 50 mg gave considerably superior analgesia (a mean duration of five days) than placebo (Budd *et al.*, 2007).

When compared to other opioids, its less constipating impact is an advantage in chronic pain disorders (Wilder-Smith *et al.*, 2009). Patient compliance is improved, and adverse effects are reduced, thanks to the oral sustained release formulation (Nossol *et al.*, 2008). There is no difference in efficacy or tolerability between twice daily tramadol 100 mg sustained release capsules and four times daily tramadol 50 mg capsules in persistent low back pain (Sorge *et al.*, 2007). Tramadol has also been shown to be beneficial in the treatment of chronic vascular pain (e.g., scleroderma) (Guseva *et al.*, 2004).

Cancer Pain

Tramadol has been demonstrated to be efficacious for the treatment of cancer pain across a wide spectrum of cancer pain syndromes, with a better side-effect profile and tolerance than morphine, and it now occupies step II of the World Health Organization ladder (Dayer *et al.*, 2007; Bamigbade *et al*., 2008). For Step I treatment, an NSAID such as paracetamol can be used, with tramadol added or substituted for insufficient analgesia or NSAID intolerance (Schnitzer et al., 2008). Overall, morphine has proved more successful for severe cancer pain in the initial treatment (which could be due to tramadol's later onset) (Bamigbade *et al.*, 2008). Tramadol has been proven to have a comparable analgesic effect to morphine and other regularly used analgesics in both cancer and non-cancer pain, while generating much fewer adverse effects (Dalgin *et al.*, 2005; Rauck *et al.*, 2004). Its significance in the long-term therapy of diverse types of intractable pain is still being better defined (Budd *et al.*, 2009).

Various combinations of Tramadol

Tramadol is frequently recommended in combination with non-opioid analgesics like paracetamol to relieve moderate to severe pain. Tramadol and paracetamol in a fixed-dose

combination provide quick onset, long duration, and multimodal analgesic effects. Tramadol (37.5 mg) plus paracetamol is administered to patients with moderate to severe acute and chronic pain (325 mg). It relieves pain for up to 8 hours longer than the medication alone in cases of dental discomfort. In postoperative dental pain, hydrocodone/paracetamol 10/650 mg has the same analgesic effect as tramadol (37.5 mg) +paracetamol during an 8-hour period (325 mg). One or two tramadol (37.5 mg) Plus paracetamol (325 mg) four times daily for five days is commonly suggested for osteoarthritis flare pain. Tramadol (37.5 mg) + paracetamol (325 mg), maximum 10 tablets or capsules per day for 4 weeks, is commonly used for chronic back pain (Lomona *et al.*, 2005; Hopkins *et al.*, 2008).

Pharmacokinetic Profile of Tramadol

Tramadol's pharmacokinetic features have been studied in limited studies in children having surgery, young and elderly healthy adults, and patients with hepatic or renal impairment.

Absorption and Distribution

Adult subjects absorbed tramadol quickly after receiving single and successive oral 100 mg doses (Abel *et al.*, 2005; Tegeder *et al.*, 2009; Lintz *et al.*, 2008). The mean absolute bioavailability of tramadol after a single oral 100 mg dose was 67.9%, and it increased to >90% when several 100 mg doses were given (Lee *et al.*, 2003; Liao *et al.*, 2002). The enhanced bioavailability of the drug with numerous oral doses may be owing to saturated first-pass hepatic metabolism, according to one theory (Lee *et al.*, 2003; Liao *et al.*, 2002). Tramadol's bioavailability was also improved when it was given with meals.

Tramadol has a significant volume of distribution after parenteral injection, indicating that it has a strong tissue affinity (Tegeder *et al.*, 2009). Although 20% of plasma proteins are bound, binding site saturation does not occur in the therapeutic dose range. Tramadol passes the placental barrier, with 80 percent of maternal amounts in umbilical venous serum (Lee *et al.*, 2003). Within 16 hours of treatment, low amounts of racemic tramadol and its M1 metabolite were identified in breast milk (Searle *et al.*, 2009).

Metabolism and Elimination

Tramadol is metabolized extensively in the liver via two primary metabolic pathways involving the isoenzymes CYP3A and CYP2D 6, with CYP2D 6 being particularly important in this drug's metabolism (Gaynes *et al.*, 2009; Paar *et al.*, 2007). Tramadol's metabolic pathway is determined by the amount of CYP2D6 sparteine-oxygenase in the liver. Tramadol is demethylated at the phenolic oxygen site in the presence of high enzyme concentrations, yielding the active M1 metabolite, whereas demethylation occurs at the amino nitrogen site in the presence of low enzyme concentrations, yielding inactive N-desmethyl tramadol (De Jong *et al.*, 2007). As a result, poor metabolisers of sparteine had considerably higher mean metabolicratios of tramadol O- demethylation than extensive metabolisers in a study of 104 healthy adult volunteers (Paar *et al.*, 2007). In phase II reactions, these O- and N-demethylated molecules (phase I reactions) may be further sulphated or glucuronidated (Gaynes *et al.*, 2009). Tramadol's elimination kinetics are best described as a two-part model, with a terminal elimination half-life of 100 mg following a single oral dose (Lintz *et al.*, 2003). The M1 metabolite had t1/2 values of 6.69 and 6.98 hours after single and multiple oral 100 mg doses,

respectively (Liao *et al.*, 2002). 90% of tramadol and its metabolites are excreted through the kidneys, with the remaining 10% passing through the feces.

Drug interactions

One of the primary causes of accidental poisoning deaths worldwide is drug interactions (Minami et al., 2004). Overdosage and a sudden combination of medicines that potentially interact with each other are the most common causes of adverse drug interactions. Precautions should be made before taking tramadol to avoid dangerous medication interactions. MAO inhibitors, antidepressants, tegretol, blood thinners, digoxin, ketoconazole, rifampin, erythromycin, quinidine, and medications that cause drowsiness are among the pharmaceuticals that interact with tramadol. It has been found to interact with 761 different medicines, causing major drug interactions in 446 cases, moderate drug interactions in 311 cases, and mild drug interactions in 4 cases. Tramadol should not be combined with alcohol, street drugs, sedatives, narcotic pain relievers, antidepressants, or anti-anxiety medications, and it should not be used to treat mental illness, bipolar disorder, or schizophrenia. Tramadol injected intramuscularly (IM) during anaesthesia reduces stomach acid output (Product Information, 2018).

Pharmacodynamic Profile of Tramadol

Mechanism of Action (MOA)

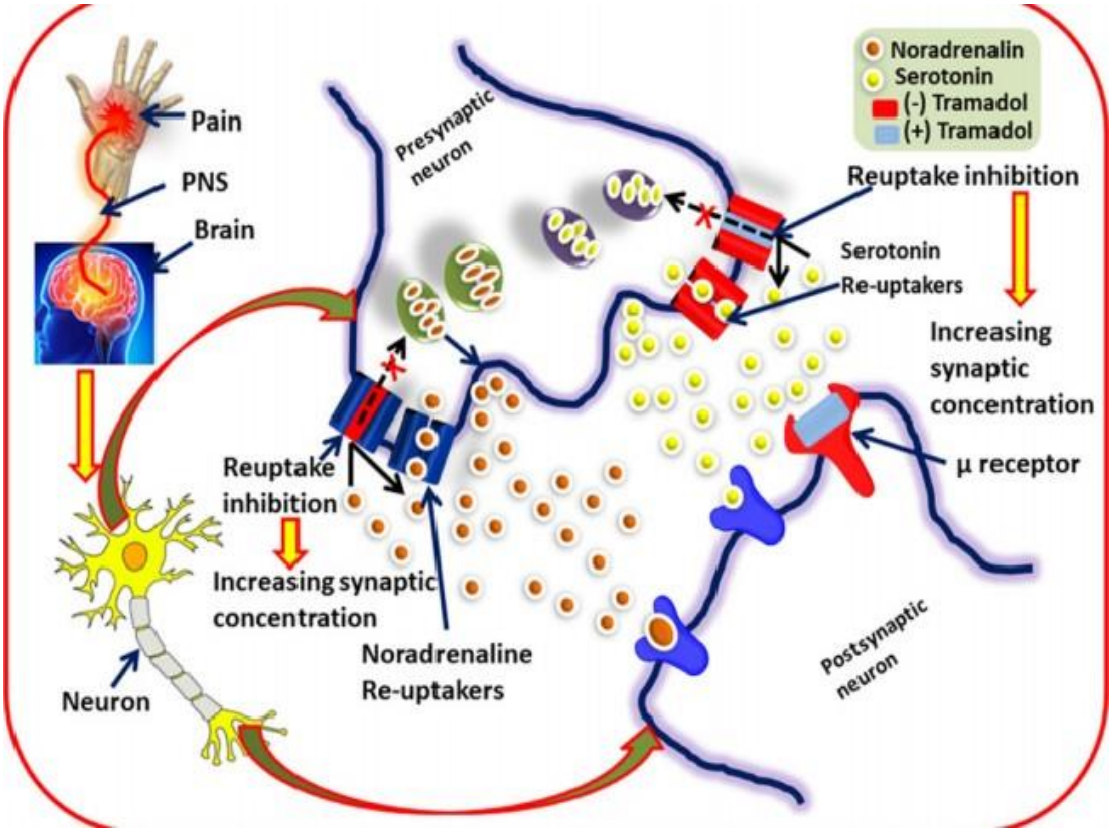

Figure 4. Schematic representation of MOA of tramadol (Scott et al., 2000)

Tramadol has a strong analgesic effect due to its central nervous system action. Tramadol's (+) dextro and (-) levo enantiomers have a synergistic analgesic effect when mixed in a racemic mixture. It works for nociception in a variety of ways, including as a mild MOR agonist or as a serotonin and norepinephrine reuptake inhibitor. Tramadol's O-desmethyltramadol metabolite (M1) has analgesic properties via acting as a weak MOR agonist. Tramadol's (+) enantiomer operates as a MOR agonist and inhibits serotonin reuptake, whereas the (-) enantiomer inhibits noradrenalin reuptake (Scott *et al.*, 2000; Minami *et al.*, 2007). There are four types of opioid receptors, all of which are G-protein coupled receptors. The majority of opioid analgesics act on the -opioid receptor. Tramadol's (+) Dextro enantiomer has Mu() opioid receptor agonistic action and enhances centraldopamine activation.

Health Implications of Tramadol

Nausea, dizziness, dry mouth, indigestion, abdominal discomfort, vertigo, vomiting, constipation, sleepiness, and headache are the most common tramadol side effects (Langley *et al.*, 2010; Keating, 2006). Interactions with other drugs may cause additional side effects. Tramadol, like morphine, has the same dose-dependent side effects, including respiratory depression (Keating, 2006).

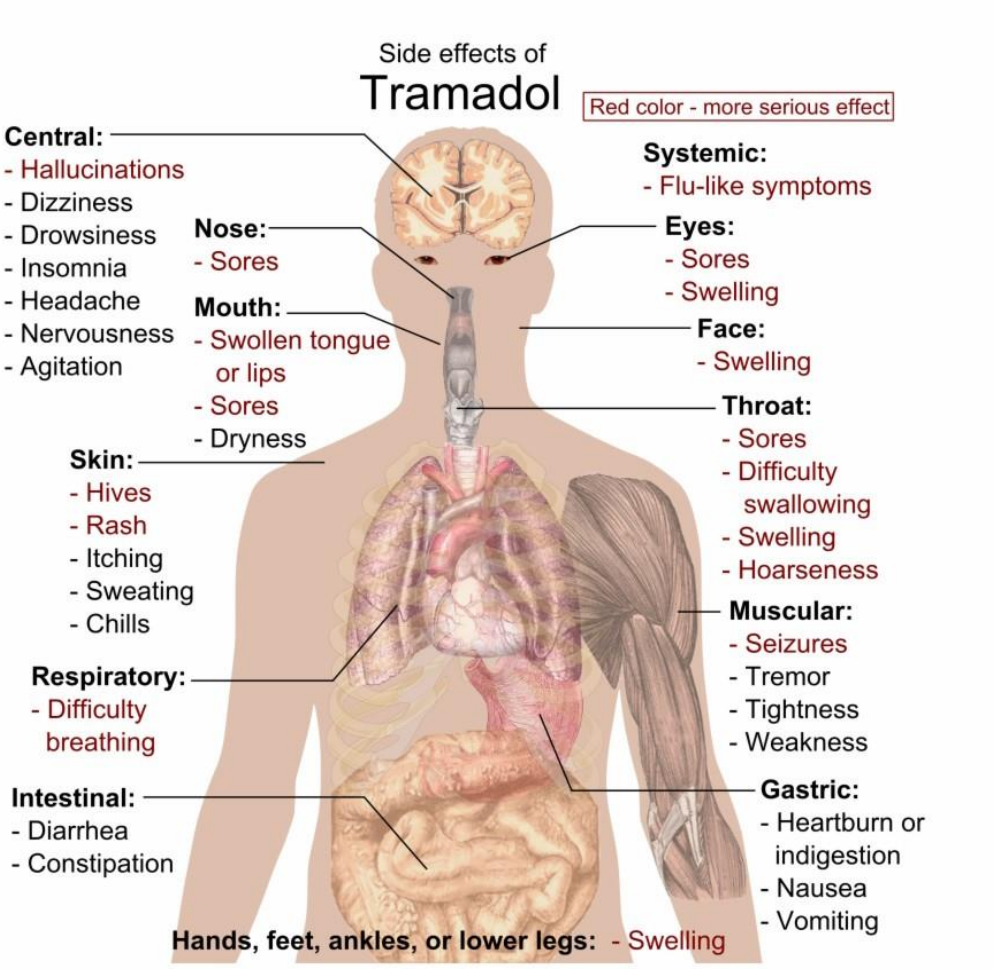

Figure 5. Main side effects of tramadol (Langley et al., 2010).

Effects on respiration

Respiratory depression is commonly related with opioid analgesics. This is mediated by a decrease in the respiratory center's sensitivity to CO_2, which leads to a reduction in respiratory rate and tidal volume (Lee *et al.*, 2003). Tramadol, unlike other opioids, is unlikely to cause clinically relevant respiratory depression at the prescribed dosage, according to evidence from trials in healthy volunteers and surgical patients. However, if the recommended dosage is significantly exceeded, respiratory depression may ensue (Spiller *et al.*, 2007). In double-blind, randomized studies including postoperative patients, the respiratory effects of tramadol were compared to those of other opioids (Houmes *et al.*, 2002; Vickers *et al.*, 2002; Langford *et al.*, 2008).

Intravenous tramadol, at a larger dose than an equianalgesic dose of morphine, temporarily slowed the pace of respiration but had no effect on end-tidal CO_2 tension, according to a dose-response research involving 30 patients (Vickers *et al.*, 2002). Using a 10:1 potency ratio for tramadol and morphine, it was determined that tramadol had a lower effect on the respiratory center than morphine (Vickers *et al.*, 2002). Furthermore, intravenous tramadol 0.6 mg/kg had similar effects on the inspiratory-expiratory oxygen difference, end-tidal CO_2 concentration, minute volume, and respiratory rate as placebo, whereas intravenous oxycodone 0.04 mg/kg caused significant respiratory depression in 36 spontaneously breathing anaesthetized patients (Tarkkila *et al.*, 2008).

Serotonin syndrome

Serotonin syndrome occurs when patients are given tramadol together with serotonin receptor inhibitors such as fluoxetine and paroxetine (Marechal *et al.*, 2011; Jeppesen *et al.*, 2006). Tramadol metabolism is inhibited by fluoxetine and paroxetine, which raises the drug's plasma levels. Serotonin syndrome is treated with agitation in the hospital and benzodiazepine therapy for seizures. Intravenous fluids are used to keep the patient hydrated (IVF). In extreme situations, the medicine that causes serotonin syndrome is stopped, and cyproheptadine (Periactin) is given to block serotonin synthesis (Graudins *et al*., 2008; Frank *et al.*, 2008).

Central nervous system

CNS stimulation, anxiety, euphoria, nervousness, sleep problem, insomnia, sadness, agitation, apathy and depersonalization, emotional liability, and in extremely rare cases, hallucinations, nightmares, dependency, and withdrawal syndrome are all prevalent mental effects of tramadol use (Barsotti *et al.*, 2003).

Dermatologic

Tramadol can induce Stevens-Johnson syndrome and hair loss in some people. Common skin problems include pruritus, perspiration, rash, dermatitis, cellulitis, piloerection, clamminess, urticaria, and toxic epidermal necrolysis.

Genitourinary

Tramadol induces menopausal symptoms and urinary tract infection in the genital system. It can induce micturition difficulties, haematuria, dysuria, cystitis, and sexual function abnormalities in some people.

Other Health Implications

Overdosing on tramadol increases the risk of seizures, thus it should be used with caution in patients who have a history of seizures or other neurologic disorders (head trauma, brain damage or CNS tumor). Naloxone treatment after an intramadol overdose may further increase the risk of seizures (Kahn *et al.*, 2007).

Acute alcohol intoxication

Tramadol is also not recommended for people who are depressed due to acute alcohol consumption. Respiratory depression and death are possible outcomes. Tramadol-induced respiratory depression is treated with Naloxone as an antidote (Vogel *et al.*, 2008).

Liver disease

The elimination time of tramadol and its metabolite M1 increases in people with severe liver cirrhosis. Tramadol should be used with caution in people who have poor liver function. Tramadol 50 mg every 12 hours is recommended for patients with liver cirrhosis (Afshari, 2009).

Renal dysfunction

Tramadol and its M1 metabolite excretion rates are lower in patients with poor renal function. In that situation, the dosage interval will be increased to 12 hours, and patients with creatinine clearance less than 30 mL/min would get a daily dose of 200 mg (Bekjarovski *et al.*, 2012). people with a clogged bile duct Tramadol 50 mg every 12 hours is recommended for patients with liver cirrhosis (Afshari, 2009).

2. CONCLUSION

Tramadol is an unusual synthetic analgesic with a wide range of applications, including acute pain, dental pain, labor pain, chronic pain, and cancer pain. Tramadol can interact with other medications that share the same metabolic pathway and employ the same enzymes, so it's important to keep track of how much tramadol patients are taking to avoid misuse and side effects.

Tramadol, on the other hand, has a lot of negative effects, thus it should be carefully chosen to treat patients, with a risk-benefit ratio in mind, and the patients should be closely watched for any possible side effects. Newer medications are needed to prevent side effects, and we propose tramadol-based derivatives for the future, with this review providing greater insights into how to build them with fewer side effects and powerful therapeutic action with minimal side effects.

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References

[1] Kidd, B.L., Langford, R.M. and Wodehouse, T. (2007). Arthritis and pain. Current approaches in the treatment of arthritic pain. *Arthritis Resources Journal,* 9: 1-7

[2] Dayer, P., Desmeules, J. and Collart, L. (2007). Pharmacology of tramadol. *Drugs,* 53(2): 18-24.

[3] Bravo, L., Mico, J.A . and Berrocoso, E. (2007). Discovery and development of tramadol for the treatment of pain. *Expert Opinion on Drug Discovery,* 12: 1281-1291

[4] Martínez, M.A., Ballesteros, S., Almarza, E. and Garijo, J. (2016). Death in a legal poppy field in Spain. *Forensic Science International,* 265: 34-40

[5] Karbakhsh, M. and Salehian, Z.N. (2007). Acute opiate overdose in Tehran: the forgotten role of opium. *Addiction Behavior,* 32: 1835-1842

[6] Zaaijer, E.R., Bruijel, J., Blanken, P., Hendriks, V., Koeter, M.W .J. and Kreek, M.J. (2014). Personality as a risk factor for illicit opioid use and a protective factor for illicit opioid dependence. *Drug Alcohol Depend,* 145: 101-105

[7] Threlkeld, M., Parran, T., Adelman, C. and Grey, S. (2006). Tramadol versus buprenorphine for the management of acute heroin withdrawal: a retrospective cohort controlled study. *American Journal of Addiction,* 15: 186-191

[8] World Health Organization, (2013). WHO's Pain Ladder for Adults, World Health Organization, Geneva, 2014 Accessed September 17, 2013 (Available from:) http://www.who.int/cancer/palliative/painladder/en/

[9] Kenzie, L.P., Donald, R.J. and Margaret, T. (2001). Abuse potential and pharmacological comparison of tramadol and morphine. *Drug Alcohol Depend,* 27: 7-17

[10] Hennies, H.H., Friderichs, E. and Schneider, J. (2008). Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. *Journal of Drug Resources*, 38: 877-880

[11] Kusari, S., Tatsimo, J., Zühlke, S., Talontsi, F.M., Kouam, S.F. and Spiteller, M. (2014). Tramadol a true natural product. *Chemical International Edition,* 53: 12059-12272

[12] Boumendjel, A., Taiwe, G.S., Bum, E.N., Chabrol, T., Beney, C., Sinniger, V., Haudecoeur,R., Marcourt, L., Challal, S., Queiroz, E.F., Souard, F. and Waard, M.D. (2013). Occurrence of the synthetic analgesic tramadol in an african medicinal plant. *Chemical International Edition,* 52: 11780-11784

[13] Lecerf-Schmidt, F., Haudecoeur, R., Peres, B., Queiroz, F.M.M., Marcourt, L., Challal, S.,Queiroz E.F., Taiwe, G.S. and Boumendjel, A. (2015). Biomimetic synthesis of tramadol. *Chemical Community* (Cambridge, U.K.), 51: 14451-14453

[14] Grond, S., Meuser, T., Zech, D., Hennig, U. and Lehmann, K.A. (2005). 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,* 62(3): 313-320

[15] Raffa, R.B., Buschmann, H., Christoph, T., Eichenbaum, G., Englberger, W ., Flores, C.M., Hertrampf, T., Kögel, B., Schiene, K., Straßburger, W., Terlinden, R. and Tzschentke, T.M. (2012). Mechanistic and functional differentiation of tapentadol and tramadol. *Expert Opinion in Pharmacothermal*, 13(10): 1437-1449

[16] Poupon, E. and Nay, B. (2011). Biomimetic Organic Synthesis, first edition, Wiley-VCH Verlag GmbH&Co, Weinheim, Germany, 2011

[17] Burke, D. and Henderson, D.J. (2002). Chirality: a blueprint for the future. *British Journal of Anaesthesia*, 88(4): 563-576

[18] Canepa, G., Di-Somma, C., Ghia, M., Vadala, A., Real, M., Cerruti, S., Stasi, M. and Trezzi, P. (2003). Post-operative analgesia with tramadol. *International Journal of Clinical Pharmacology Resources*, 13: 43-51

[19] Malik, A., Kaul, R. and Kaul, V. (2015). Clinical effectiveness of three analgesic formulations on post- operative endodontic pain: a Pilot study. *International Journal of Therapy Application*, 25: 7-11

[20] Sunshine, A. (2004). New clinical experience with tramadol. *Drugs*, 47: 8-18

[21] Yilmaz, M.Z., Torun, C., Sarihasan, B.B., Kelsaka, E., Koksal, E., Tas, N. and Kuruoglu, E. (2015). Comparison of the analgesic effects of paracetamol and tramadol in lumbardisc surgery. *Turkish Journal of Medical Science,* 45: 438–442

[22] Hussein, O.A., Adel, I.M . and Kadhim, A.A. (2015). Efficacy of combined tramadol with diclofenac in comparison with monotherapy treatment using Buscopan Diclofenac or tramadol in renal pain control. *Medical Journal of Baby,* 12: 1070–1074

[23] Bloor, M., Paech, M.J. and Kaye, R. (2012). Tramadol in pregnancy and lactation. *International Journal of Obstetric Anesthesia*, 2: 163–167

[24] James, M.F.M., Heijke, S.A.M., and Gordon, P.C. (2006). Intravenous tramadol versus epidural morphine for post-thoracotomy pain relief: a placebo- controlled double-blindtrial. *Anesthetic and Analgesic,* 83: 87-91

[25] Lomona, J. (2005). Is tramadol a suitable analgesic for high risk patients after heart surgery? *Britain Journal of Anaesthetic*, 74(2): 7

[26] Kupers, R., Callebaut, V., Debois, V., Camu, F., Verbogh, C., Coppejars, H. and Adriansen, H. (2005). Efficacy and safety of oral tramadol and pentazocine for post-operative pain following prolapsed intervertebral disc repair. *Anaesthesiology in Belgium*, 46: 31-37

[27] Hopkins, D., Shipton, E.A. and Potgieter, D. (2008). The comparison of tramadol and morphine by subcutaneous PCA. *Canadian Journal of Anaesthetic*, 45: 435-442

[28] Rud, V., and Fischer, M.V. (2004). Postoperative analgesia with tramadol: continuous in fusion versus repetitive bolus administration. *Anaesthetist*, 43: 316-321

[29] Barsoum, M.W . (2005). Comparison of the efficacy and tolerability of tramadol, pethidine, and nalbuphine in children with postoperative pain. *Clinical Drug Investment*, 9: 183-190

[30] Bosenberg, A. and Ratcliffe, S. (2008). The respiratory effects of tramadol in child renunder halothanean aesthesia. *Anaesthesia,* 53: 960-964

[31] McQuay, H.J. and Moore, R.A. (2008). Postoperative analgesia and vomiting, with special reference today-case surgery: a systematic review. *Health Technology Assessment,* 2: 1-236

[32] Lehmann, K.A. (2007). Tramadol in acute pain. *Drugs,* 53(2): 25-33

[33] Bamigbade, T.A. and Langford, R.M. (2008). The clinical use of tramadol hydrochloride. *Pain Reviews,* 5: 155-182

[34] Duthie, D.J.R. (2008). Remifentanil and tramadol. *Britain Journal of Anaesthetic,* 81: 51-57

[35] Vickers, M.D. and Paravicini, D. (2005). Comparison of tramadol with morphine for post-operative pain following abdominal surgery. European Journal of Anaesthesiology, 12: 265-271

[36] W ilder-Smith, C.H., Hill, L., Osler, W . and O'Keefe, S. (2009). Effect of tramadol andmorphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. *Digestive Disease Science,* 44: 1107-1116

[37] De-Witte, J., Deloof, T., de-Veylder, J. and Housemans, P.R. (2007). Tramadol in the treatment of post-anaesthetic shivering. *Anaesthesiology,* 41: 506-510

[38] Chan, A.M., Ng, K.F., Tong, E.W. and Jan, G.S. (2009). Control of shivering under regional anesthesia in obstetric patients with tramadol. *Canadian Journal of Anaesthetic,* 46: 253-258

[39] Budd, K. and Langford, R. (2009). Tramadol revisited. *Britain Journal of Anaesthetic,* 82: 493-495

[40] Mackin, G.A. (2007). Medical and pharmacologic management of upper extremity neuropathic pain syndromes. *Journal of Hand Resources,* 10: 96-109

[41] Harati, Y., Gooch, C. and Swenson, M. (2008). Double-blind randomised trial of tramadol for the treatment of the pain of diabetic peripheral neuropathy. *Neurology*, 50: 1842-1846

[42] Roth, S. (2008). Efficacy and safety of tramadol hydrochloride in breakthrough musculoskeletal pain attributed to osteoarthritis. Journal of Rheumatology, 25: 45-54

[43] Biasi, G., Manca, S., Manganelli, S. and Marcolongo, R. (2008). Tramadol in the fibromyalgia syndrome: a controlled clinical trial versus placebo. *International Journal of Clinical Pharmacology Resources,* 18: 13-19

[44] Nossol, S. (2008). Treatment of pain with sustained-release tramadol. *International Journal of Clinical Practise, 52*: 94-126

[45] Sorge, J. and Stadler, T. (2007). Comparison of the analgesic efficacy and tolerability of tramadol 100 mg sustained-release tablets and tramadol 50 mg capsules for the treatment of chronic lowback pain. *Clinical Drug Investment*, 14: 157-164

[46] Schnitzer, T.J. (2008). Non-NSAID pharmacologic treatment options for the management of chronic pain. *American Journal of Medicine,* 195(1): 45-52

[47] Dalgin, P.H. (2005). Use of tramadol in chronic pain. *Clinical Geriatrics,* 3: 1-6

[48] Abel, S.R. (2005). Tramadol: an alternative analgesic to traditional opioids and NSAIDs. *Journal of Pharmaceutical Care and Pain Symptom Control,* 3(1): 5-29

[49] Tegeder, I., Lötsch, J. and Geisslinger, G. (2002). Pharmacokinetics of opioids in liver disease. *Clinical Pharmacokinetic,* 37: 17-40

[50] Lintz, W., Barth, H. and Osterloh, G. (2008). Pharmacokinetics of tramadol and bioavailability of enteraltramadol formulations. 3rd communication: suppositories. *Clinical Pharmacy,* 48: 889-899

[51] Lee, C.R., McTavish, D. and Sorkin, E.M. (2003). Tramadol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs,* 46: 313-340

[52] Liao, S., Hills, J. and Stubbs, R.J. (2002). The effect of food on the bioavailablity of tramadol. *Pharmaceutical Resources,* 9: 308

[53] Gaynes, B.I. and Barkin, R.I. (2009). Analgesics in ophthalmic practice: a review of theoral non-narcoticagent tramadol. *Visual Science,* 76: 455-461

[54] De Jong, R.H. (2007). Comment on the hypoalgesic effect of tramadol in relation to CYP2D6 [comment]. *Pain Digestion,* 7(4): 245

[55] Paar, W.D ., Poche, S. and Gerloff, J. (2007). Polymorphic CYP2D 6 mediates O-demethylation of the opioid analgesic tramadol. *European Journal of Clinical Pharmacology,* 53: 235-239

[56] Barkin, R.L. (2005). Focus on tramadol: a centrally acting analgesic for moderate to moderately severe pain. *Formulary,* 30: 321-325

[57] Minami, K., Uezono, Y. and Ueta, Y. (2007). Pharmacological aspects of the effects of tramadol on G-protein coupled receptors. *Journal of Pharmacological Science,* 103: 253-260

[58] Scott, L.J. and Perry, C.M. (2000). Tramadol: a review of its use in perioperative pain. *Drugs,* 60(1): 139-176

[59] Langley, P.C., Patkar, A.D., Boswell, K.A., Benson, C.J. and Schein, J.R. (2010). Adverseevent profile of tramadol in recent clinical studies of chronic osteoarthritis pain. *Current Medical Research and Opinion,* 26(1): 239-251

[60] Keating, G.M. (2006). Tramadol sustained-release capsules. *Drugs,* 66(2): 223-230

[61] Spiller, H.A., Gorman, S.E. and Villalobos, D. (2007). Prospective multicenter evaluation of tramadol exposure. *Journal of Toxicology and Clinical Toxicology,* 35: 361-364

[62] Houmes, R.M., Voets, M.A. and Verkaaik, A. (2002). Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. *Anesthetic and Analgesic,* 74: 510-514

[63] Langford, R.M., Bakhshi, K.N. and Moylan, S. (2008). Hypoxaemia after lower abdominal surgery: comparison of tramadol and morphine. *International Journal of Acute Pain Management*, 1: 7-12

[64] Tarkkila, P., Tuominen, M. and Lindgren, L. (2008). Comparison of respiratory effects of tramadol and pethidine. *European Journal of Anaesthesiology*, 15: 64-68

[65] Marechal, C., Honorat, R. and Claudet, I. (2011). Serotonin syndrome induced by tramadol intoxication in an 8-month-old infant. *Pediatric Neurology*, 44: 72-74

[66] Jeppesen, U. Gram, L.F. and Vistisen, K. (2006). Dose- dependent inhibition of CYP1A 2, CYP2C19, and CYP2D 6 by citalopram, fluoxetine, fluvoxamine and paroxetine. *European Journal Pharmacology*, 51: 73-78

[67] Frank, C. (2008). Recognition and treatment of serotonin syndrome. *Canadian Family Physiology*, 54: 988-992

[68] Barsotti, C.E., Mycyk, M.B. and Reyes, J. (2003). Withdrawal syndrome from tramadol hydrochloride. *American Journal of Emergency Medicine*, 21: 87-88

[69] Kahn, L.H., Alderfer, R.J. and Graham, D.J. (2007). Seizures reported with tramadol. *Journal of American Medicine and Anatomy*, 278: 1661

[70] Vogel, W ., Burchardi, H., Sihler, K. and Valic, L. (2008). The respiratory and circulatory effects of tramadol. *Drug Resources*, 28: 183-186

[71] Afshari, R. and Ghooshkhanehee, H. (2009). Tramadol overdose induced seizure, dramatic rise of CPK and acute renal failure. *Journal of Pakistan Medicine Association*, 59: 178

[72] Bekjarovski, N., Chaparoska, D. and Radulovikj-Bekjarovska, S. (2012). Seizures after use and abuse of tramadol. *Prilozi*, 33: 313-318