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The Dangerous Effects of Tramadol Abuse: Literature Review

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ABSTRACT

Drug abuse is an act of using one or a combination of drugs in relatively high doses with the aim not for medication but to achieve a pleasure without regard to other aspects. Drug abuse can be motivated by several factors such as a weak personality, a high sense of curiosity, peer invitations, social problems and pressures, and the ease with which drugs can be obtained at low prices. One of the drugs that is often abused is tramadol. This is because tramadol can provide a euphoric effect. Without realizing it, tramadol abuse actually causes other, more dangerous effects. Therefore, writing this review article aims to provide an overview of other effects resulting from the abuse of tramadol drugs. The writing of this article review uses a systematic review method in which data is taken from national and international scientific articles or journals with a limitation of publication in the last 10 years. Articles obtained from searches using Google Scholar, PubMed, and Science Direct. From the results of the review, it is known that the misuse of tramadol drugs can be fatal because it can cause vomiting, seizures, sedation, and even death. Not only that, tramadol in high doses also affects fertility factors such as sperm defects and erectile dysfunction. Special attention is needed for cases of tramadol abuse because most of these activities are carried out by teenagers.

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1. INTRODUCTION

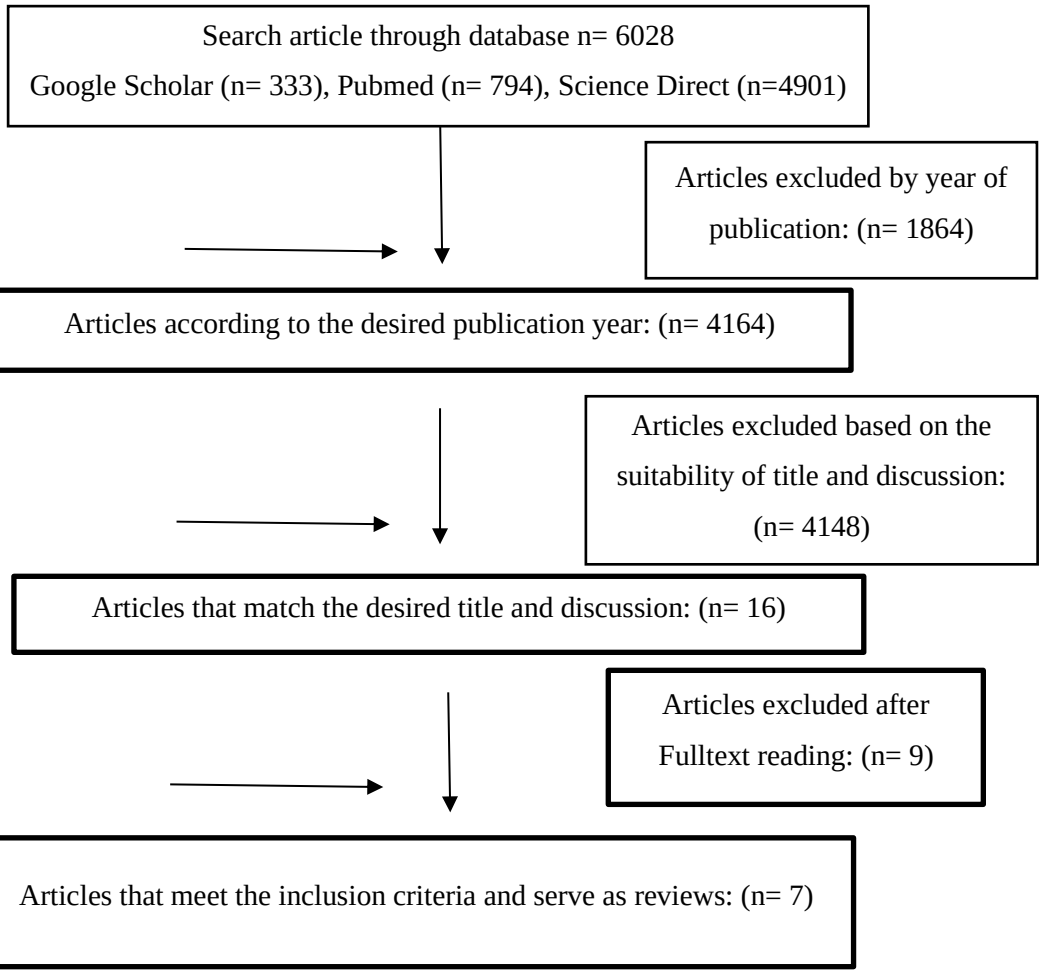
Drug abuse is an act of using one or a combination of drugs in relatively high doses with the aim not for medication but to achieve a pleasure without regard to other aspects. Drug abuse can have physical, psychological, and social effects [1]. According to the Regulation of the Head of BPOM No. 28 of 2018, drugs that are often abused are drugs that act on the Central Nervous System (CNS) structure such as dextromethorphan, haloperidol, amitriptyline, chlorzapine, tramadol, and trihexyphenidyl [2]. These drugs if abused regularly will cause various effects such as addiction and changes in the user's mental, behavioral, emotional activities. The act of drug abuse can occur due to several factors such as weak personality, high sense of curiosity, invitation from peers, problems and social pressure, and ease of obtaining drugs at low prices [3].

One of the drugs that is often abused is tramadol. Tramadol is a synthetic, centrally acting opioid analgesic. Tramadol is metabolized in the liver to CYP2D6-mediated O-desmethyl-tramadol and CYP3A4-mediated N-desmethyltramadol by conjugation reactions resulting in glucuronide and sulfate [4]. Based on data from the Indonesia Drug report, in 2019 there were 844 cases of drug abuse where the most abused drug was tramadol, which was 129 cases [5]. Tramadol abuse occurs at various ages with various purposes. In adults, this drug is consumed with the aim of relieving stress and social pressure [6]. Meanwhile, among teenagers, this drug is consumed with the aim of giving calm and euphoria [7].

The recommended daily dose of tramadol is 50-100 mg every 4-6 hours. The maximum allowable dose is 400 mg/day [8]. In the right dose, tramadol can provide an analgesic effect. While at higher doses, tramadol can provide the same side effects as certain narcotics in the form of euphoria. In addition to these effects, the consumption of tramadol in high doses can produce more harmful effects [7]. Based on the explanations that have been presented, the purpose of writing this review article is to provide an overview of other effects resulting from the abuse of tramadol drugs.

2. METHOD

This article using a systematic review method was used where the data obtained were a collection of several related articles. The articles or journals used in this review article are national and international scientific journals with a limit of publication in the last 10 years. Article searches were conducted on the Internet from Google Scholar, PubMed, and Science Direct using the keywords "drug abuse", "tramadol abuse", "Tramadol abuse". From the database search process, 6028 articles were generated. There were 1864 journals that were excluded due to non-compliance with the criteria for the desired journal publication year, namely the last 10 years. Then as many as 4148 journals were re-excluded due to incompatibility with the desired title and discussion, namely tramadol abuse. A total of 9 journals were re-excluded after reading the entire contents of the journal. So it was found as many as 7 articles that met the inclusion requirements, namely discussing the effects of tramadol abuse and used as a review.



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3. RESULTS AND DISCUSSION

Table 1. Contains data from a review of 7 articles regarding the discussion of the harmful effects of tramadol abuse

Penulis dan Tahun	Judul Penelitian	Obat yang disalahgunkan	Dosis	Efek
(Ferrari et al., 2014)	Tramadol Abuse in a Binge Pattern in a Young Depressed Woman.	Tramadol & diazepam	300-500 mg/day with the highest dose taken 850 mg/day, Diazepam 2 mg/day	Addiction and tolerance. At lower doses patients experience depression, anxiety, nervousness, abdominal pain, dry mouth, nausea, vomiting, constipation & urinary retention. Numbness in specific areas, sweating, intense fatigue, loss of appetite, insomnia & tachycardia. The patient does not complain of seizures
(Gioia et al., 2017)	Two Fatal Intoxications Due to Tramadol Alone	Tramadol	Tramadol 32 g/mL in cardiac blood, 23.9 g/mL in femoral blood, 3.3 g/mL in bile, and 1.4 g/mL in urine and 7.5 g/mL in cardiac blood, 5, 8 g/mL in femoral blood, and 18 g/mL in urine	Poisoning caused the death.
(Barbera et al., 2013)	A suicidal poisoning due to tramadol. A metabolic approach to death investigation	Tramadol	Dosage or levels: tramadol concentration in femoral blood was 61.83 mcg/ml & carbamazepine concentration in femoral	Acute death due to poisoning caused of consumption tramadol with doses that are too high.

			blood was 3.2 mg/L	
(Farag et al., 2018)	Tramadol (opioid) abuse is associated with a dose- and time-dependent poor sperm quality and hyperprolactinaemia in young men	Tramadol	3 x 225 mg/days	Decreased semen quality and vitality, progressive decrease in motility, high incidence of leukocytospermia, and abnormal sperm defects. The hormonal profile is also disturbed where there is a significant increase in the hormones FSH, LH and prolactin (hyperprolactinemia) with low androgen levels.
(Bassiony et al., 2019)	Sexual Dysfunction among Male Patients with Tramadol abuse: A Case-Control Study	Tramadol	Tramadol > 450 mg/days	Erectile dysfunction, reduction of penile hyperexcitability & prolongation of sensory conduction. Decreased domains of orgasm, sexual desire, and sexual satisfaction.
(Bassiony et al., 2020)	Free Testosterone and Prolactin Levels and Sperm Morphology and Function Among Male Patients WithTramadol Abuse	Tramadol	Tramadol 225-3375 mg with an average use of 900 mg/day	Decreased testosterone levels and increased prolactin levels. Decreased sperm, vitality and motility and higher abnormal sperm.
(Shamloul et al., 2020)	Tramadol-associated seizures in Egypt: Epidemiological, clinical, and radiological study	Tramadol alone and with benzodiazepine marijuana, alcohol	225-1800 mg/day with a mean of 783 mg/day.	Idiopathic seizures or epilepsy. Depression

Tramadol is a hard drug (G) which is included in the type of Certain Drugs (OTT) or in other words its circulation is under strict supervision because it is often misused [15]. At therapeutic doses, tramadol produces an analgesic effect, while at high doses it causes a euphoric effect and delays ejaculation. This is the background that tramadol is often abused by teenagers and adults. Tramadol abuse can cause several adverse effects such as dependence and changes in mental activity and behavior of users [16]. Effects that usually occur after consuming high doses of tramadol include excess euphoria, headache, sweating, dry mouth, nausea, vomiting, and sedation. Then the effects are exacerbated by the

onset of angioedema, tachycardia, seizures, serotonin syndrome, decreased pulse rate, difficulty breathing and death [7].

Tramadol is a synthetic opioid analgesic that acts centrally as a pain reliever for chronic and acute pain. For description, tramadol is in the form of white crystals that are odorless and have a bitter taste. Tramadol is soluble in water and ethanol. Tramadol has a structure in the form of trans-2 (dimethylaminomethyl)-1-(m-methoxyphenyl)-cyclohexanol hydrochloride which is the development of aminocyclohexanol which is an opioid agonist [4]. The allowable oral therapeutic dose for tramadol is 50-100 mg every 6 hours with a maximum dose of 400 mg/day [7]. The range of concentrations of tramadol in blood is for a therapeutic effect of 0.1-0.8 mcg/ml, a toxic effect of 1-2 mcg/ml, and a lethal effect of 2 mcg/ml or higher. Increasing the dose every time will cause dependence where the administration of tramadol at a dose of 800 mg / day can provide the same dependence as morphine [9] Tramadol works to produce an analgesic effect in the Central Nervous System (CNS) where in producing an analgesic effect, tramadol works synergistically as a mu-opioid receptor agonists and monoamic serotonin & norepinephrine reuptake inhibitors (SNRIs). The analgesic effect of tramadol is thought to be due to the presence of 2 chiral centers, namely R, R-enantiomer ([+]–Tramadol) which is the most potent serotonin reuptake inhibitor and S, S-enantiomer ([-]–Tramadol) is a norepinephrine & serotonin reuptake inhibitor, so that there will be an increase in noradrenergic and serotonergic activity when both compounds work [17].

Tramadol has 2 active metabolites namely O-desmethyltramadol and N-desmethyltramado which act on (mu) opioid receptors to produce an analgesic effect [18]. The metabolic process of the two active metabolites is assisted by the CYP450 314 and 2D6 isoenzymes where CYP2D6 is in charge of producing O-desmethyltramadol compound through the O-demethylation process, and CYP3A4 & CYP2B6 in charge of producing N-desmethyltramadol through the N-demethylation process. Furthermore, the two metabolites were conjugated to glucuronide and sulfate [4].

The active metabolite O-desmethyltramadol acts as a major player in producing an analgesic effect (Bima Ardika Putra et al., 2019). It has a high affinity for (mu) opioid receptors [18] with a half-life of about 7.4 hours and a volume of distribution of 3 L/kg [19]. But behind its role, the active metabolite O-desmethyltramadol is thought to be the main cause in cases of fatal tramadol poisoning which can result in death [18]. This is related to the metabolic process of these metabolites mediated by the CYP2D6 isoenzyme where most of the CYP2D polymorphisms have poor metabolism, causing drug accumulation. Drug accumulation will increase the duration of action and the risk of drug side effects that lead to toxicity [1]. Deaths related to tramadol poisoning are generally due to potential interactions with other drugs such as benzodiazepines, barbiturates, antidepressants, and alcohol. But in cases of suicide, a single tramadol overdose causes respiratory depression resulting in death [10]. Respiratory depression that occurs due to excessive stimulation of the 2 (mu) receptor as a result of the high dose of tramadol causing a decrease in acetylcholine levels in the medulla area which affects the response to CO2 [9]. Administration of tramadol at high doses causes several adverse effects. One of them is the seizurogenic or convulsive effect which is thought to occur due to the inhibition of aminobutyric acid (GABA) [14]. Administration of diazepam is thought to reduce the potential for seizures [8]. While the effects of nausea and vomiting are thought to be due to excessive stimulation of dopaminergic receptors in the Chemo Trigger Zone (CTZ) of the brain [18].

Prolonged abuse of high doses of tramadol can cause impaired action of the hypothalamic-pituitary-adrenal system (APH) and hypothalamic-pituitary-gonadal system (HPG) through binding to opioid receptors in the hypothalamus and pituitary gland [13]. The SNRI properties of tramadol are thought to be the main cause of this problem where high doses of tramadol will cause hyperprolactinism which affects hypogonadism and a decrease in testosterone precursors, namely dehydroepiandrosterone. The destruction of testosterone precursors will affect sperm quality in the form of an increase in abnormal shape and a decrease in sperm motility and vitality. Administration of tramadol in toxic doses will increase nitric oxide (NO) and testicular lipid peroxidation on testosterone secretion in Leydig cells [11]. The delaying effect of premature ejaculation due to high doses of tramadol is thought to be related to the effects of serotonin reuptake and neuronal inhibition in the lumbar spinothalamic region [12]. In

addition, NMDA receptors through the mechanism of lumbosacral spinal inhibition and inhibition of M1 & M3 muscarinic acetylcholine receptors also play a role in the effect. Meanwhile, the effect of delaying penile erection is thought to be through the inhibition of noradrenaline and serotonin reuptake at peripheral opioid receptors and involves Nitric Oxide (NO) [19]. Basically tramadol abuse is motivated by several reasons, especially stress. Therefore, in order to help tarmadol abusers to be free from addiction, it is necessary to approach the heart, provide attention, and social support to perpetrators from family, friends, or community leaders in the surrounding environment [16]. As a preventive measure, providing information and counseling about the dangers of tramadol abuse and providing religious knowledge is also considered very important. Meanwhile, curative measures can be carried out through rehabilitation and treatment under the supervision of medical personnel [1].

4. CONCLUSION

The effect of tramadol depends on the dose of use where when tramadol is taken at the right therapeutic dose it will produce an analgesic effect, while at high doses it will produce a euphoric effect and delay ejaculation. Tramadol abuse can be fatal because it can cause vomiting, seizures, sedation, and even death. Not only that, tramadol in high doses also affects fertility factors such as sperm defects and erectile dysfunction. Special attention is needed for cases of tramadol abuse because most of these activities are carried out by teenagers. Preventive actions that can be taken are through giving attention, inculcating religious knowledge, and counseling about the dangers of tramadol abuse. As for curative measures, rehabilitation and treatment can be carried out under the supervision of medical personnel/

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