SAÚDE E PESQUISA
e-ISSN 2176-9206

ORIGINAL ARTICLE

https://doi.org/10.17765/2176-9206.2025v18e13273

CHARACTERISTICS AND FACTORS RELATED TO TRAMADOL ABUSE: AN INTEGRATIVE REVIEW

CARACTERÍSTICAS E FATORES RELACIONADOS AO ABUSO DE TRAMADOL: UMA REVISÃO INTEGRATIVA

Maira Jeane da Silva[1], Ana Cláudia de Brito Passos[2], Edilson Martins Rodrigues Neto[3*], Mirian Parente Monteiro[4], Maria Augusta Drago Ferreira[5]

[1] Pharmacist from the Federal University of Ceara, Fortaleza (CE) Brazil,[2] PhD in Pharmaceutical Sciences, Pharmacist at the Department of Pharmacy at the Federal University of Ceará, Fortaleza (CE), Brazil, [3] PhD in Pharmacology. Professor of the postgraduate programs in Development and Technological Innovation in Medicines at the Federal University of Ceará - PPGDITM UFC and Biotechnology - PPGBIOTEC UECE, Fortaleza (CE), Brazil. [4] Full professor at the Department of Pharmacy at the Federal University of Ceará, Fortaleza (CE), Brazil. [5] Associate Professor IV of the Department of Pharmacy at the Federal University of Ceará, Fortaleza (CE), Brazil.

***Corresponding author**: Edilson Martins Rodrigues Neto – **Email:** edilsonmrneto@hotmail.com

Received: 24 Oct. 2024
Accepted: 21 Dec. 2024

ABSTRACT: The evidence found in the literature on the abusive use of tramadol and its motivations was described. This is an integrative review carried out in the PubMed, Scopus and Virtual Health Library databases, using the descriptors "tramadol" and "abuse". Eleven studies were selected, published between January 1, 2013 and December 31, 2022, and 82% of these were from African countries. The individuals who abused tramadol were predominantly male, aged between 13 and 45 years, and in 63% of the studies, they had at least a high school education and in 72.2% they worked. The motivations were: influence of friends, pain relief, improvement of mood and sexual performance. Regarding tramadol dependence, 45.45% of the individuals were in treatment. The results of the review mainly reflect the situation of some African countries that have a notable abusive use of tramadol.
KEYWORDS: Tramadol. Abuse. Integrative review.

RESUMO: Foram descritas as evidências encontradas na literatura sobre o uso abusivo de tramadol e suas motivações. Trata-se de uma revisão integrativa realizada nas bases de dados PubMed, Scopus e Biblioteca Virtual em Saúde, utilizando os descritores "tramadol" e "abuso". Foram selecionados 11 estudos, publicados entre 1º de janeiro de 2013 e 31 de dezembro de 2022, sendo que 82% destes eram de países africanos. Os indivíduos que abusaram de tramadol eram predominantemente do sexo masculino, com idade entre 13 e 45 anos, e em 63% dos estudos possuíam no mínimo ensino médio e em 72,2% trabalhavam. As motivações foram: influência de amigos, alívio da dor, melhora do humor e desempenho sexual. Em relação à dependência de tramadol, 45,45% dos indivíduos estavam em tratamento. Os resultados da revisão refletem principalmente a situação de alguns países africanos que apresentam um uso abusivo notável de tramadol.
PALAVRAS-CHAVE: Tramadol. Abuso. Revisão integrativa.

INTRODUCTION

The non-medical use of opioids has grown alarmingly. Currently, they are included among the main drugs subject to abuse in some countries, such as the United States of America (USA). For some years now, the U.S.A. has been experiencing one of its worst crises, largely generated due to the use of a synthetic opioid, fentanyl, which led to the declaration of a public health emergency in 2017. Approximately 74,000 opioid overdose deaths were recorded in the U.S.A. over a period of one year, from April 2020 until April 2021 [1,2].

In 2021 alone, opioids accounted for two-thirds of the 585,000 drug-related deaths worldwide, according to the United Nations Office on Drugs and Crime (UNODC). This alarming statistic highlights the devastating impact of opioids, including tramadol, a drug increasingly misused in certain regions [3].

Although the crisis experienced by the U.S.A. is highlighted, other countries also face the problem of opioid abuse by their inhabitants. Thus, some countries in Africa have remarkable rates of this kind of use, with studies evincing that addiction cases and overdose deaths due to tramadol have become increasingly frequent [2]. According to the World Drug Report of the United Nations Office on Drugs and Crime (UNODC) for the year 2021, tramadol abuse is a serious public health problem in these countrie [3].

Opioid use disorder (OUD) can be defined as the loss of control over opioid use, leading to constant cravings for use, the development of tolerance, and withdrawal crises. Based on eleven defined criteria, the Diagnostic and Statistical Manual for Mental Disorders - 5th edition (DSM-5) classifies this disorder into different levels in terms of its severity. Thus, the fulfillment of two to three of these criteria is considered a mild disorder, four to five moderate and six or more it is indicative of severe disorder [4].

According to the UNODC report (2023), for the year 2021, there were about 60 million opioid users worldwide. In addition, two-thirds of the 585,000 drug-related deaths that occurred that year were caused by opioids [3].

Developed in the 1970s in Germany, the toxic effects of tramadol, especially the most severe ones, such as respiratory depression due to overdose and dependence, manifest themselves less intensely compared to other opioids [5].

It should be noted that tramadol is a prodrug and the metabolite O-desmethyltramadol, its main biotransformation product, has an affinity for opioid receptors about 300 times greater than the original compound. Compared to morphine, the analgesic activity of tramadol is much lower [6].

Tramadol was the first synthetic opioid, capable of producing the analgesic effect through two main mechanisms of action. One of them, common to the other drugs of the opioid class, is its action as an agonist of opioid receptors, and the other consists into nociception modulation, by acting as a reuptake of the neurotransmitters serotonin and noradrenaline inhibitor, thus also being useful in controlling neurogenic pain [5].

The use of tramadol can cause adverse effects common to opioids, and the most reported are nausea, dizziness, constipation, headaches, and drowsiness. Moreover, it can also produce further serious toxic effects like serotonin syndrome, seizures, and addiction. The risk of tramadol inducing addiction is considered low when compared to other opioids, and this is one of the factors that enabled its widespread use. However, studies have shown that although it is low, this risk cannot be ignored [7].

Withdrawal symptoms for tramadol are similar to those of other opioids, individuals often present sweating, tremor, anxiety, diarrhea, bone, muscle, and abdominal pain, and psychotic symptoms have also been reported [8]. Currently, there is no protocol developed exclusively for the treatment of tramadol dependence. However, treatment for opioid dependence consists of gradual

dose reductions of the substance or its replacement by an opioid agonist, with methadone being the drug of choice used in Brazil for the treatment of opioid dependence [9].

This study aimed to describe the evidence found in the literature on the abusive use of tramadol and its motivations.

METHODOLOGY

This is an integrative review carried out according to the method described by Botelho, Cunha and Macedo (2011) [10], which comprises six stages. The PICo framework guided the formulation of the research questions and the selection criteria, ensuring that the studies focused specifically on humans (P), tramadol misuse (I), and its motivational factors and adverse effects within diverse social contexts (Co).

The search process and the selection of studies were carried out by two researchers simultaneously. In cases of divergence, a consensus was sought with a third researcher involved in the study.

The analysis stage began with the translation, reading and interpretation of the articles results. The articles characterization was performed by extracting the following information: author and year of publication, title of the article, type and purpose of the study, and country of origin. Subsequently, the results were presented in three different tables, with data obtained from the studies, taking into account the variables arranged in the following categories: (1) sociodemographic characteristics (gender, age, education level and occupation) of the study participants who abused tramadol; (2) characteristics of tramadol abuse (circumstance of use, route of administration and dosage of tramadol, method of diagnosis, form of addiction treatment, and manifestation of adverse effects associated with tramadol abuse).

RESULTS

The results of adopted procedures for the studies selection included in this review are presented in Figure 1.

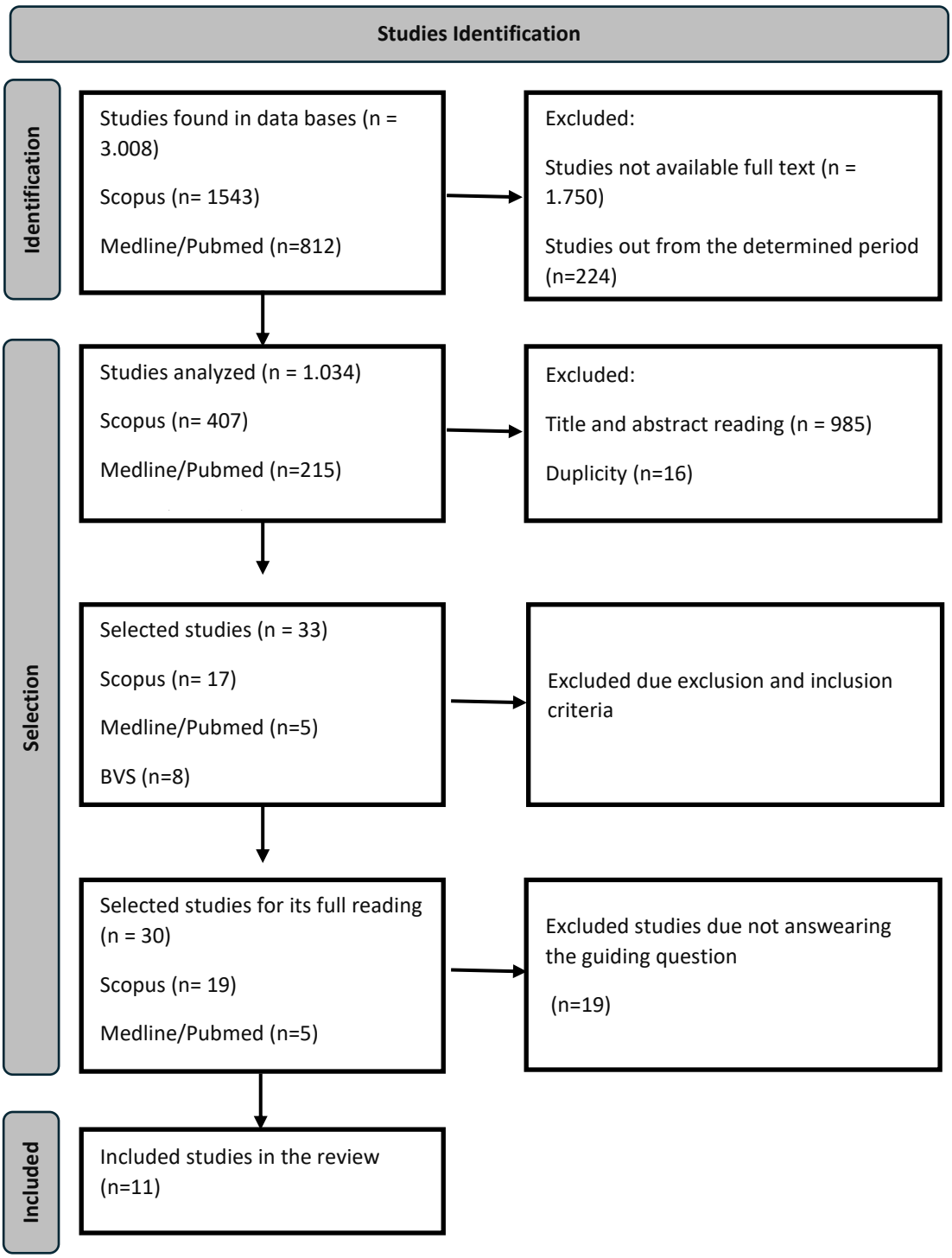

Figure 1 - Selection of studies included in the integrative review according to the Prisma recommendation.
Source: Made by the author (2023).

Information about the articles included in this review, author and year of publication, title of the article, type and objective of the study, and country of origin are shown in Table 1.

Table 1 - Information (author and year of publication, title of the article, type and objective of the study, and country of origin) gathered from the studies included in the integrative review. Fortaleza-CE, 2013 to 2022.

Author and Year	Article title	Study type	Country	Study objective
Abdel-Moneim., *et al* 2022 [11]	Association Between Male Sex Hormones And Tramadol Abuse	Control Case	Egypt	To identify possible hormonal changes in males who abused tramadol.
Danso M; Anto F, 2021 [12]	Factors Associated With Tramadol Abuse: A Cross Sectional Study Among Commercial Drivers And Assistants In The Accra Metropolitan Area Of Ghana	Analytical cross-sectional	Gana	Elucidate factors associated with tramadol abuse by drivers and their assistants.
Saapiire F., *et al* 2021 [13]	The Insurgence Of Tramadol Abuse Among The Most Active Population In Jirapa Municipality: A Study To Assess The Magnitude Of The Abuse And Its Contributory Factors	Analytical cross-sectional	Gana	To identify the magnitude of tramadol abuse among active individuals in a city, and to analyze the motivating factors of this use.
Elrassas HH., *et al* 2021 [14]	Cognitive Impairment In Patients Diagnosed With Tramadol Dependence Compared To Healthy Controls	Comparative cross-sectional	Egypt	To compare 30 healthy subjects with 30 tramadol users to estimate the prevalence of possible impairment in users.
Diab M., *et al* 2020 [15]	Risk And Protective Factors Of Tramadol Abuse In The Gaza Strip: The Perspective Of Tramadol Abusers And Psychiatrists	Qualitative	Palestine	To report the perceptions of addicts and psychiatrists involved in their treatment about the associated factors to tramadol abuse.
Abd-Elkader., *et al* 2020 [16]	Tramadol Abuse Among Workers In An Industrial City In Mid-Nile Delta Region, Egypt	Cross-sectional	Egypt	Define the profile of workers who abused tramadol and the motivations for this use.
Peprah P., *et al* 2020 [17]	"With Tramadol, I Ride Like A Jaguar": A Qualitative Study Of Motivations For Nonmedical Purpose Tramadol Use Among Commercial Vehicle Operators In Kumasi, Ghana	Qualitative Exploratory	Gana	To define the profile of workers who used tramadol abuse and the motivations for this use.
Fuseine A., *et al* 2019 [18]	Facilitators To The Continuous Abuse Of Tramadol Among The Youth: A Qualitative Study In Northern Ghana	Descriptive Exploratory Qualitative	Gana	To investigate the factors associated with tramadol abuse among young people.
Bassiony MM., *et al* 2018 [19]	Opioid Use Disorders Attributed To Tramadol Among Egyptian University Students	Cross-sectional	Egypt	To describe the profile of university students who misused tramadol and to identify the factors associated with this use.
Bassiony., *et al* 2015 [20]	Adolescent Tramadol Use And Abuse In Egypt	Cross-sectional	Egypt	To investigate the prevalence of tramadol misuse among adolescents.
Zhang H; Liu Z, 2013[21]	The Investigation Of Tramadol Dependence With No History Of Substance Abuse: A Cross-Sectional Survey Of Spontaneously Reported Cases In Guangzhou City, China	Cross-sectional	China	To analyze tramadol's potential to cause addiction among individuals who had no history of other substance abuse

Table 1 shows that, among the articles published between January 1st, 2013 and December 31, 2022, only 11 were included in the present study, most of which came from African countries, Egypt (n=5; 45.0%) and Ghana (n=4; 36.0%).

Table 2 - Information about the individuals participating in the analyzed studies (tramadol abuse, gender, age, education level, and occupation), 2013 to 2023, Fortaleza-CE.

INDIVIDUALS CHARACTERISTICS					
Article	**Prevalence of tramadol abuse**	**Gender**	**Age (years)**	**Education level**	**Occupation**
Abdel-Moneim., *et al* 2022 [11]	**67** (50,0%)	Men (100%)	25 - 35 (56,7%)	Technical courses (46,3%)	Self-employed (58,2%)
Danso M; Anto F, 2021 [12]	**114** (24,9%)	Men (100%)	21 - 30 (65,0%)	High school /Graduate (51,7%)	Driver assistant (58,7%)
Saapiire F., *et al* 2021 [13]	**118** (28,1%)	Men (90,7%) Women (9,0%)	18 - 25 (39,8%)	High school (37,3%)	Self-employed (57,6%)
Elrassas HH., *et al* 2021 [14]	**30** (50,0%)	Men (100%)	18 - 45 (50,0%)	High school (63,3%)	Employed (73,3%)
Diab M., *et al* 2020 [15]	**13** (100,0%)	Men (100%)	24 - 34 (69,2%)	Graduate (30,8%) High school (30,8%)	Employed (84,6%)
Abd-Elkader., *et al* 2020 [16]	**512** (56,9%)	Men (100%)	20 - 29 (52,3%)	-	Construction (54,1%)
Peprah P., *et al* 2020 [17]	**23** (100,0%)	Men (86,9%) Women (13,1%)	18 - 30 (39,2%)	-	Driver (65,2%) Assistant (34,7%)
Fuseine A., *et al* 2019 [18]	**18 (**100,0%)	Men (83,3%) Women (16,7%)	18 - 25 (72,2%)	Elementary school (61,1%)	-
Bassiony MM., *et al* 2018 [19]	**21** (1,8%)	Men (76,2%) Women (23,8%)	17 - 34 (100%)	-	Student
Bassiony., *et al* 2015 [20]	**15** (7,4%)	Men (100%)	13 - 18 (100%)	High school (15.1%)	Student
Zhang H; Liu Z, 2013[21]	**23** (100%)	Men (100%)	18 - 34 (23,4%)	High school and graduate (60,9%)	Employed (69,6%)

The variables analyzed results with the purpose of characterizing the individuals participating in the studies included in the review, contained in Table 2, show that among the individuals who abused tramadol use, the male gender was predominant and individuals age ranged from 13 to 45 years old. In 63.6% of the studies, the individuals had completed at least high school and in 72.2% of the studies, most of the individuals who abusively used tramadol, performed some work activity.

Regarding the variables analyzed in order to characterize the abusive use of tramadol, the route used for its administration was oral in all studies analyzed. Only Abdel-Moneim et al. (2022) reported the use of the intravenous route by about 20.9% of the participants in their study [11].

The studies included in the review that reported on the dose of tramadol used by individuals who abusively used tramadol are described below. Elrassas et al. (2021) reported that 1125 mg/day was the highest dose of tramadol used by these individuals in their study [14].

Danso and Anto (2020) [12] reported that these individuals in their study referred to the drug dosage, mentioning the physical characteristics of the tablets containing tramadol or the purpose of its use, as described below. "Tramadol is 225, blue is 120, and we also have 150, which is the aphrodisiac, and 120 which is D-10." According to Saapiire et al. (2021) [13], most of the interviewees in their study did not know the dose of tramadol they used.

Several motivating factors for the abusive use of tramadol were reported in the studies, highlighting, among others, the influence of friends, mitigating the physical consequences of work and

being able to cope with activities, treat diseases, maintain mood and for the purpose of improving sexual performance.

Table 3 shows the different methods of diagnosis and forms of treatment for tramadol dependence, as well as the clinical manifestation (signs and symptoms) of toxic effects reported in the analyzed studies.

Table 3 - Information on the diagnosis and treatment of dependence and adverse effects due to tramadol abuse reported in the studies analyzed. Fortaleza-CE, 2013 to 2022.

Article	Tramadol dependence diagnostic	Dependence treatment	Adverse effects manifestations
Abdel-Moneim., *et al* 2022 [11]	[2]DSM-IV	Attendance at a drug addiction management unit	-
Danso M; Anto F, 2021 [12]	[1] Screening Test for Involvement with Alcohol, Smoking, and Other Substances	-	-
Saapiire F., *et al* 2021 [13]	Questionnaire - Self-report	-	-
Elrassas HH., *et al* 2021 [14]	[2]DSM-IV	Addiction treatment unit care	-
Diab M., *et al* 2020 [15]	Patients in mental health center	Treatment by community mental health program	-
Abd-Elkader., *et al* 2020 [16]	[2]DSM-V	The individuals were interested in being treated	-
Peprah P., *et al* 2020 [17]	Self-report	Individuals did not report interest in treating themselves	Seizures Vomiting Anorexia Loss of appetite Hallucination Severe nausea Agitation and confusion Drowsiness Dry mouth Generalized pains Weakness Redness and itching of the skin Sweating Swelling in the extremities Tremors
Fuseine A., *et al* 2019 [18]	Patients in a psychiatric unit undergoing rehabilitation due to dependence	Inpatient treatment	Vomiting Nausea Loss of appetite Anorexia
Bassiony MM., *et al* 2018 [19]	[4]DUDIT	-	-
Bassiony., *et al* 2015 [20]	[4]DUDIT	-	-
Zhang H; Liu Z, 2013[21]	[2]DSM - IV Opiate Withdrawal Scale - physical dependence [3]ARCI-CV - psychological dependence	Inpatient treatment	Seizures Tearing Insomnia

1 Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) developed by the WHO.
2 Diagnostic and Statistical Manual of Mental Disorders (DSM), prepared by the American Psychological Association (APA)
3 Addiction Research Center Inventory–Chinese Version Association Test (ARCI-CV)
4 Drug Use Disorders Identification Test (DUDIT)
Source: Made by the author (2023).

For the tramadol abuse and dependence diagnosis, the studies used questionnaires pre elaborated, which were filled out according to the individuals' answers. In 45.4% of the studies, participants were receiving inpatient treatment or in detoxification centers. Only three studies reported adverse effects associated with tramadol abuse.

DISCUSSION

The studies included in this review sought to answer the following questions: what is the profile of individuals who abuse tramadol, under what circumstances does this use occur, and what motivating factors and adverse effects are associated with tramadol abuse?

According to the results obtained, it was observed that the majority (82%) of the articles included in the present study comes from African countries. This finding can be explained, at least in part, by information contained in the UNODC World Drug Report for the year 2021. That report warned about the serious crisis related to opioid abuse, and mentioned that non-medical use of opioids, especially tramadol, has shown remarkable rates in West African countries, Central and Northern, where there is a growing illegal trade in this drug [3].

The reasons that led to the crisis related to the non-medical use of tramadol, which is now present in some African countries, are not entirely clear, but it may be related to this drug availability and the lack of usage regulation. Large-scale production and low cost in the market make tramadol attractive to individuals operating illicitly in the market (drugs traffickers). In addition, the fact that it is a drug, available for sale in pharmacies, it does not carry the stigma of other substances that can be abused [3].

The availability of opioids in Latin America compared to other countries, for example, the United States is more limited. However, opioid consumption has increased in countries such as Brazil, Argentina, Colombia, Chile and Uruguay. In Brazil, between 2009 and 2015, the number of prescriptions containing opioids increased from 1.601.043 to 9.045.945 [22]. Nevertheless, during the process of searching for the articles selected for this review, the scarcity of studies on opioid abuse, conducted in Brazil was revealed, and no studies on tramadol abuse were found.

When investigating the sociodemographic characteristics of individuals who abused tramadol, a notable predominance of males was observed in all studies included in this review. Corroborating this finding, the U.S. National Survey on Drug Use and Health showed that in 2016 and 2017, opioid misuse in all age groups analyzed was higher among males. In addition, between 2015 and 2017, there was an increase in fatalities due the use of opioids by individuals of both genders, but a higher rate was observed among men, especially in the age group of 25 to 44 years [23].

The abusive use of tramadol aiming sexual performance improvement and premature ejaculation treatment were reported by participants from the study by Abdel-Moneim et al. (2022)[11]. According to these authors, some of these individuals explained that after long workloads it was difficult to perform well sexually, and others reported that sometimes their partners themselves acquired and offered tramadol to be used.

According to Saleh; Majzoub; El-Hamd (2019)[24], premature ejaculation is one of the sexual dysfunctions that most affect men and, among other causes of this dysfunction, psychological and genetic factors, endocrine alterations, urological conditions and drug use are included.

Based on the results obtained in their meta-analysis study, Sharma et al. (2021)[25] reported that although some studies demonstrate some efficacy associated with the use of tramadol for

premature ejaculation treatment, the results need to be evaluated with caution, as this use is also related to adverse events including hormonal changes and dependence. According to these authors, most of the studies analyzed did not evaluate the risk associated with this objective of usage, and reported that additional investigations are necessary in order to determine the minimum dose necessary for tramadol to produce this effect effectively and safely.

Sociocultural factors associated with gender should also be considered. Some countries still impose stigmas on women and their roles, which can interfere with substance use or experiencing addiction reports [23]. According to Diab et al. (2020) [15], the absence of women in their study may be related to the great stigma placed on this gender, mainly due to religious norms. Thus, even if they abused tramadol, many women did not seek treatment, nor did they seek help for fear of admitting to being addicted to substance use.

Regarding the age group, the results obtained in the present study showed that the abusive use of tramadol occurred mainly among adolescents and young adults of different ages, who sought the effects attributed to this substance, such as getting "high", especially by young people [18,20] or for the relief of pain associated with occupation, improvement of sexual performance, and treatment of premature ejaculation by older men [11,12,17].

The survey by Cardoso and Malbergier (2014)[26], reported the use of psychoactive substances among adolescents can be influenced by friends, especially when acceptance is sought within groups, in which there is a positive stimulus for abuse. Friendship with supportive individuals who use drugs is a strong predictor of abuse in adolescence. Adolescents who, in their groups of friends, live with illicit drug users are more exposed and consequently have more opportunities to use them [27].

The constant stress to which an individual is exposed causes physical and psychological effects that, on a daily basis, interfere with the fulfillment of their obligations and interpersonal relationships [28]. In his study, conducted with drug users at a Psychosocial Care Center for Alcohol and Other Drugs (CAPS AD), these authors observed that the main stressors among the population studied were related to work and the responsibility of family supporting, and discussed that, in view of this, the search for escape mechanisms is common and one of the most used is the substances usage that alleviates this tension state, such as tramadol.

The educational level of individuals who abused tramadol varied among the studies analyzed. Thus, most of the study participants from Ghana had a high school education, with the exception of Fuseine et al. (2019) [18]. In this study, the participants had elementary education and in the other studies they had higher education or technical education.

Regarding the occupation of individuals who abusively used tramadol in the studies examined, it was observed that most of them were employed or self-employed, performing functions that required a high level of physical effort and long workloads, under low remuneration. As an example, the study by Abd-Elkader et al. (2020) [16], conducted with textile and construction workers and drivers, showed that the highest percentage of tramadol abuse occurred among construction workers and was associated with the nature of this occupation.

In the studies carried out in Ghana, the main occupations reported by the workers were drivers and their assistants, and one of the alleged reasons for the abusive use of tramadol was to fulfill demands required by this profession. Hakim; Mohsen (2017) [29] reported that, among drivers, who need to spend long periods in the same position and work long hours, the risk of manifesting lower back pain is around 50%, which reveals the lack of ergonomics, commonly associated with this work activity.

According to Fiuza et al. (2022) [30], about 14 deaths resulting from road accidents are recorded in Brazil daily. Several factors are pointed out as the cause of these occurrences, including the

precariousness of the highways, violation of traffic laws and the drugs consumption. Among the substances used by drivers, especially truck drivers, the use of opioids is reported for pain relief due to the long periods in which these professionals remain seated. However, it is known that opioids can cause drowsiness, an extreme risk factor for traffic accidents.

In line with a report by Danso and Anto (2021) [12], although tramadol is on the list of drugs considered to have a high potential for abuse by the Ghanaian Food and Drugs Authority (FDA), and is subject to several types of control to obtain it, the participants in their study reported that the illegal market, friends, and licensed or unlicensed chemical stores are acquisition sources of this drug. According to these authors, due to the ease of obtaining and low price of tramadol in this circumstances, many workers, even without a prescription, use it for pain relief and compliance with their workloads.

When analyzing the variables considered to characterize the abusive use of tramadol by the participants of the studies included in the present review, it was observed that, predominantly, the oral route used for its administration. The availability of tramadol and the ease of administration are the main reasons for the increased use of tramadol by this route.5 The use of the intravenous route was also reported by Abdel-Moneim et al. (2022)[11], but as the responsible for the analgesic effect attributed to tramadol is O-desmethyltramadol (M1), its main metabolite, the use of the intravenous route, by avoiding first-pass metabolism and the consequent formation of M1, leads to the loss, in part, of the effects produced by this opioid. There is also a report in the literature about the use of crushed tramadol tablets nasally, believing that this may increase its bioavailability [25].

Regarding the highest dose of tramadol (1125 mg/day) used by participants in the study by Elrassas et al. (2021) [14], who abused this drug, it is much higher than the usual recommended doses. In the immediate-release formulation of tramadol, the maximum recommended dose is 400 mg/kg/day, and for extended-release capsules the maximum recommended daily dose is 300 mg/kg. Use above these dosages and without medical supervision is considered improper, and can cause serious harmful effects, including seizures [5].

Different factors can lead an individual to misuse substances. In the case of opioids, it is common for this use aiming the pain relievement or the feeling of euphoria. However, the rapid development of tolerance to the effects produced by these drugs can result in the dependence development [31]. Dependence presents itself by signs and symptoms, including the manifestation of an abstinence crisis after abrupt drug withdrawal. In this context, different procedures can be adopted for the diagnosis of dependence.

Two of the studies included in this review were based on self-reports by the interviewees, namely that of Saapiire et al. (2021)[13] and that of Peprah et al. (2020)[17]. Although it is not completely reliable, as it is not a diagnosis made by a qualified professional, the self-report is based on the individual's observation of himself, his attitudes and the consequences caused, which provides a critical opinion. An individual's awareness of their addiction state is an important step that leads to seeking help and treatment.

It was observed that among the studies analyzed, only those by Peprah et al. (2020)[17], Fuseine et al. (2019)[18] and Zhang[21] brought reports of patients who manifested toxic effects arising at some point from the abusive use of tramadol. The most cited were severe vomiting, lack of appetite and anorexia. There were reports of patients who had seizures in two of these studies, while in the study by Fuseine et al. (2019)[18], individuals who abusively used tramadol, together with friends, reported never having suffered seizures, but had witnessed their occurrence in friends.

Constipation, drowsiness, nausea, vomiting and dry mouth associated with tramadol use reveal common adverse effects produced by opioid drugs. However, serotonin syndrome and seizures are serious effects, which occur mainly in situations of misuse and abuse of these drugs. According to the

individuals reports who used tramadol abusively, in the participants of studies included in the present review, tramadol adverse effects were perceived as being caused by the initial doses, since they decreased significantly with the continuation of use. For this reason, some individuals who decided to discontinue the use of tramadol gave up, in the face of information given by friends, that these effects would disappear with the use continuation. Vomiting and nausea could persist even with long periods of use, so when taking tramadol, individuals did not drink anything other than water or soda, so as not to feel ill when taking the pills. Reported anorexia is a secondary manifestation, because in these cases, individuals did not eat before ingesting the drug or lost their appetite after using it [17,18,21].

By virtue of centrally acting opioids be able to lower the seizure threshold, there is a greater risk of this effect being produced by tramadol [32,33]. By comparing tramadol with tapentadol, a centrally acting synthetic opioid structurally similar to tramadol, Roulet et al. (2021)[7] in their study showed that seizures occurred more frequently among individuals who used tramadol, which can happen as early as the first 24 hours after its administration. Another important factor is that seizures can occur, both in the supratherapeutic dose range and in the therapeutic dose range [5].

Regarding the treatment for tramadol abuse or dependence, it was observed that the participants of practically all studies were already being treated in a hospital environment, in centers designated for addicts. The research conducted by Abd-Elkader et al. (2020)[16], participants expressed interest in receiving treatment. On the contrary, in the study by Peprah et al. (2020)[17], the individuals interviewed reported that they would only stop using tramadol if a new drug with the same effects emerged.

In general, the treatment for opioid use disorder is composed of psychological and pharmacological approaches. Psychological treatment seeks to help the patient deal with and understand their situation, in addition to offering support, in order to reduce feelings of exclusion and loneliness and avoid relapses. Pharmacological treatment is mainly based on the replacement of the substance on which the individual is dependent by another opioid agonist drug, which acts longer and has less potential for abuse, with the purpose of alleviating withdrawal symptoms. Among others, methadone is the drug of choice for this use [34].

Although studies have shown a low potential for tramadol to cause dependence, it was possible to verify its occurrence when evaluating the studies included in the present review. The UNODC report already treats tramadol abuse as a growing crisis, especially in African continent countries and, as previously described, the use of this drug is motivated by its availability and low cost, characteristics that make it capable of reaching other countries. Misuse or abuse of tramadol was considered to be that in which individuals used it without a medical prescription or obtained it illegally. However, it is known that even with a prescription, misuse can occur. In addition, prescriptions may be made without a better evaluation of the possible use of drugs with minor undesirable effects [3].

According to Miotto et al. (2017)[3], it has been shown that this drug has a greater potential for abuse when associated with other drugs or drugs that potentiate its effects, such as alcohol, benzodiazepines, and other analgesics. In addition, it can be a gateway to other substances abuse. In view of the above, it is necessary to carry out further studies that can evaluate the tramadol ability to act alone as a substance of abuse or in association with other substances.

The evidence found in this review presents relevant practical implications as it highlights the predominant characteristics of users and the motivations for the abusive use of tramadol, providing information for a better understanding of this context.

CONCLUSION

The obtained results with the present study are in line with data made available in the latest UNODC report on the current tramadol abuse crisis. The profile of individuals who abused tramadol consisted mainly of men, age groups corresponding to adolescents and young adults, as well as in cases of other substances usage. The reasons related to tramadol abuse were multifactorial, involving psychological, financial, family and other conditions.

Brazil has a high unemployment rate, low wages, and a high rate of substance abuse, and opioids are present in this context. As previously mentioned in this study, prescriptions containing tramadol have increased along recent years in several countries, including Brazil. It should be noted that there are no studies that address tramadol abuse in the country, which leaves a gap on how this problem currently presents itself.

In view of this, the greater availability of this drug makes it possible to increase the diversion of use or its misuse. As in the aforementioned countries, in which the tramadol use is a cause for concern, it is necessary to carry out studies in Brazil on the abusive use of tramadol, the incidence of dependence and other harmful effects associated with this use.

Therefore, it is necessary to consider strategies to prevent the abusive use of tramadol, as well as regulatory measures and/or clinical recommendations aimed at prescribers.

REFERENCES

1. Britch SC, Walsh SL. Treatment of opioid overdose: Current approaches and recent advances. Psychopharmacology [Internet]. 2022 Apr 7;239(7):2063–81. https://doi.org/10.1007/s00213-022-06125-5
2. Degenhardt L, Grebely J, Stone J, Hickman M, Vickerman P, Marshall BDL, et al. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. Lancet (London, England) [Internet]. 2019;394(10208):1560–79. https://doi.org/10.1016/S0140-6736(19)32229-9
3. UNODC. World Drug Report 2021. 2021 Disponível em: https://www.unodc.org/unodc/en/data-and-analysis/wdr2021.html.
4. Kosten TR, Baxter LE. Review article: Effective management of opioid withdrawal symptoms: A gateway to opioid dependence treatment. The American Journal on Addictions. 2019 Jan 31;28(2):55–62. https://doi.org/10.1111/ajad.12862
5. Miotto K et al. Trends in Tramadol: Pharmacology, Metabolism, and Misuse. Anesthesia & Analgesia. 2017; 124(1): 44-51. https://doi.org/10.1213/ANE.0000000000001683
6. Minami K, Ogata J, Uezono Y. What is the main mechanism of tramadol? Naunyn-Schmiedeberg's Archives of Pharmacology [Internet]. 2015 Oct 1;388(10):999–1007. https://doi.org/10.1007/s00210-015-1167-5
7. Roulet L, Rollason V, Desmeules J, Piguet V. Tapentadol Versus Tramadol: A Narrative and Comparative Review of Their Pharmacological, Efficacy and Safety Profiles in Adult Patients. Drugs. 2021 Jul;81(11):1257–72. https://doi.org/10.1007/s40265-021-01515-z
8. Shafi A, Berry AJ, Sumnall H, Wood DM, Tracy DK. Synthetic opioids: a review and clinical update. Therapeutic Advances in Psychopharmacology. 2022 Jan;12:204512532211396. https://doi.org/10.1177/20451253221139616
9. Melo AP de, Fujii YWH, Rangel MP, Nishida FS. RETIRADA DE OPIOIDES: uma revisão bibliográfica / OPIOID WITHDRAWAL: a literature review. Brazilian Journal of Development [Internet]. 2020 Sep 10;6(9):67098–112. https://doi.org/10.34117/bjdv6n9-227

10. Botelho LLR, Cunha CCA, Macedo M. O método da revisão integrativa nos estudos organizacionais. Gestão e Sociedade. 2011; 5(11): 21-136. Available from: https://d1wqtxts1xzle7.cloudfront.net/77319808/1220-Texto_do_artigo-641-4530-10-20111202.pdf_filename_UTF-81220-Texto_do_artigo-641-4530-10-20111202-libre.pdf?1640442693=&response-content-disposition=inline%3B+filename%3DO_Metodo_Da_Revisao_Integrativa_Nos_Estu.pdf&Expires=1729562084&Signature=IImPe~izt-v9CHWAD5oS6Jn0ohHMNs6lIKudwJBIlwjM29gxHK1k74dZYNvoNWJ-sfOmcEDsEK-AZUN22F6YN3-LidVpWiSsB8MfOynoQkTZTYVjo1trCkx1VENrZDEwkL7lM-Qclsa75GXdJWAdctui3OnFcl-v41dpPH8RUmnin1GXBM9trEqIvbGNmh2mz2csEHeuET~LkM2mpJrw~rw7HUWNDDDbQbys8KCc5~H~GKS6DNzH~PdDTgrfN4xMdRFziPF5WjuCtS8Rk7gbfdaDgJSQR3el5RQabVY5L4OWQN0rrII~r6rRezgDDVAtATVoyTn1qavDWsbPAhSFkA__&Key-Pair-Id=APKAJLOHF5GGSLRBV4ZA
11. Abdel-Moneim WM, Fawzy M, Mohammed SA, Abdellah NZ. Association between male sex hormones and tramadol abuse. Middle East Current Psychiatry. 2022 Apr 29;29(1). https://doi.org/10.1186/s43045-022-00199-9
12. Danso M, Anto F. Factors Associated with Tramadol Abuse: A Cross-Sectional Study Among Commercial Drivers and Assistants in the Accra Metropolitan Area of Ghana. Drugs - Real World Outcomes. 2021 Apr 28. https://doi.org/10.1007/s40801-021-00247-6
13. Saapiire F, Namillah G, Tanye V, Abubakari A. The Insurgence of Tramadol Abuse among the Most Active Population in Jirapa Municipality: A Study to Assess the Magnitude of the Abuse and Its Contributory Factors. Grutsch J, editor. Psychiatry Journal. 2021 Feb 5;2021:1–10. https://doi.org/10.1155/2021/3026983
14. Elrassas HH, Elsayed YA, El Nagar ZM, Abdeen MS, Mohamed AT. Cognitive impairment in patients diagnosed with tramadol dependence compared to healthy controls. International Clinical Psychopharmacology [Internet]. 2020 Oct 29 [cited 2024 Oct 22];36(1):38–44. https://doi.org/10.1097/YIC.0000000000000340
15. Diab M, Veronese G, Jamei YA, Kagee A. Risk and Protective Factors of Tramadol Abuse in the Gaza Strip: The Perspective of Tramadol Abusers and Psychiatrists. International Journal of Mental Health and Addiction. 2020 Jun 11. https://doi.org/10.1007/s11469-020-00301-4
16. Abd-Elkader MR, Kabbash IA, El-Sallamy RM, El-Sawy H, Gad ESAH. Tramadol abuse among workers in an industrial city in mid-Nile Delta region, Egypt. Environmental Science and Pollution Research. 2020 Mar 2;27(30):37549–56. https://doi.org/10.1007/s11356-020-08040-8
17. Peprah P, Agyemang-Duah W, Appiah-Brempong E, Akwasi AG, Morgan AK. "With tramadol, I ride like a Jaguar": a qualitative study of motivations for non-medical purpose tramadol use among commercial vehicle operators in Kumasi, Ghana. Substance Abuse Treatment, Prevention, and Policy. 2020 Jul 23;15(1). https://doi.org/10.1186/s13011-020-00292-4
18. Fuseini A, Afizu A, Yakubu YH, Nachinab G. Facilitators to the continuous abuse of tramadol among the youth: A qualitative study in Northern Ghana. Nursing Open. 2019 Jul 30;6(4):1388–98. https://doi.org/10.1002/nop2.353
19. Bassiony MM, Abdelghani M, Salah El-Deen GM, Hassan MS, El-Gohari H, Youssef UM. Opioid Use Disorders Attributed to Tramadol Among Egyptian University Students. Journal of Addiction Medicine [Internet]. 2018;12(2):150–5. https://doi.org/10.1097/ADM.0000000000000380
20. Bassiony MM, Salah El-Deen GM, Yousef U, Raya Y, Abdel-Ghani MM, El-Gohari H, et al. Adolescent tramadol use and abuse in Egypt. The American Journal of Drug and Alcohol Abuse. 2015 Apr 10;41(3):206–11. https://doi.org/10.3109/00952990.2015.1014959
21. Zhang H, Liu Z. The Investigation of Tramadol Dependence with No History of Substance Abuse: A Cross-Sectional Survey of Spontaneously Reported Cases in Guangzhou City, China. BioMed Research International. 2013;2013:1–6. https://doi.org/10.1155/2013/283425
22. Servin ETN, Filipe LNSM, Leal P da C, Oliveira CMB de, Moura ECR, Gomes LMR de S. The world crisis of use of opioids in non-oncological chronic pain: causes and management strategies and

relationship with Brazil. Brazilian Journal of Health Review. 2020;3(6):18692–712. https://doi.org/10.34119/bjhrv3n6-259
23. Fattore L, Marti M, Mostallino R, Castelli MP. Sex and Gender Differences in the Effects of Novel Psychoactive Substances. Brain Sciences. 2020 Sep 3;10(9):606. https://doi.org/10.3390/brainsci10090606
24. Saleh R, Majzoub A, Abu El-Hamd M. An update on the treatment of premature ejaculation: A systematic review. Arab Journal of Urology. 2021 Aug 4;1–22. https://doi.org/10.1080/2090598X.2021.1943273
25. Sharmaa P et al. Safety and efficacy of "on-demand" tramadol in patients with premature ejaculation: an updated meta-analysis. International Braz J Urol, [S.L.], v. 47, n. 5, p. 921-934, out. 2021. FapUNIFESP (SciELO). https://doi.org/10.1590/S1677-5538.IBJU.2020.056
26. Cardoso LRD, Malbergier A. A influência dos amigos no consumo de drogas entre adolescentes. Estudos de Psicologia (Campinas) [Internet]. 2014 Mar;31(1):65–74. https://doi.org/10.1590/0103-166X2014000100007
27. Piehler TF, Véronneau MH, Dishion TJ. Substance Use Progression from Adolescence to Early Adulthood: Effortful Control in the Context of Friendship Influence and Early-Onset Use. Journal of Abnormal Child Psychology [Internet]. 2012 Apr 18;40(7):1045–58. https://doi.org/10.1007/s10802-012-9626-7
28. Dalpiaz AK, Helena M, Daniele K, Bolson MP, Hirdes A. Factors associated with the use of drugs: Statements from users of a CAPS AD/Fatores associados ao uso de drogas: depoimentos de usuarios de um CAPS AD. Revista Aletheia [Internet]. 2014 Sep [cited 2024 Oct 24];(45):56–72. Disponível em: https://pepsic.bvsalud.org/pdf/aletheia/n45/n45a05.pdf
29. Hakim S, Mohsen A. Work-related and ergonomic risk factors associated with low back pain among bus drivers. Journal of Egyptian Public Health Association [Internet]. 2017 Dec 1;92(3):195–201. https://doi.org/7.10.21608/EPX.2018.16153
30. Fiuza LMP, Freitas LPP, Flipone NG, Silva PF. O uso de opioides e anfetaminas por caminhoneiros e seus efeitos neurofisiológicos. Revista FT. 2022: 1-6. https://doi.org/10.5281/zenodo.7378310
31. Ahmed AI, Khalifa El-Dawy, Fawzy MM, Abdallah HA, Elsaid A, Elmesslamy WO. RETROSPECTIVE REVIEW OF TRAMADOL ABUSE. Slov Vet Res 2018; 55 (Suppl 20): 471–83. https://doi.org/10.26873/SVR-677-2018
32. Wang S. Historical Review: Opiate Addiction and Opioid Receptors. Cell Transplantation. 2019 Nov 13;28(3):233–8. https://doi.org/10.1177/0963689718811060
33. Beakley BD, Kaye AM, Alan David Kaye. Tramadol, pharmacology, side effects, and serotonin syndrome: A review [Internet]. Scholarly Commons. 2015. Disponível em: https://scholarlycommons.pacific.edu/phs-facarticles/534/
34. Silva ERCT, Moura MMA, Siqueira EC.Transtornos relacionados ao uso de opioides | Revista Eletrônica Acervo Saúde. acervomaiscombr [Internet]. 2024 Apr 15; https://doi.org/10.25248/reas.e14637.2024