THE USE AND ABUSE OF TRAMADOL AMONG ADOLESCENTS AND YOUNG ADULTS, AND THE NEED FOR REGULATION, ADDIS ABABA, ETHIOPIA

A Thesis Submitted to the Department of Pharmaceutics and Industrial Pharmacy, School of Pharmacy, Addis Ababa University in partial fulfillment for the requirements of Master of Science Degree in Regulatory Affairs (Medicine Stream)

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This is to certify that the thesis prepared by Abebe Telila Berru, entitled "the use and abuse of tramadol among adolescents and young adults, and the need for regulation" submitted in partial fulfillment for the requirements of master of science degree regulatory affairs (medicine stream) complies with the regulations of the university and meets the accepted standards concerning originality and quality.

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Abstract

The use and abuse of tramadol among adolescents and young adults, and the need for regulation

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Background: Tramadol was originally approved as non-controlled drug, as it is claimed to have weak opioid properties and a low dependence potential. Recent studies, however, indicated that there is an increased abuse potential, making tramadol abuse a significant public health risk. As a result, there is a trend to recognize tramadol as a controlled substance by regulators in many countries. The situation in Ethiopia is not clear, forming the rationale for initiating this study.

Objective: The objective of this study was to assess the use and abuse of tramadol as well as the need for its regulation in Addis Ababa.

Materials and Method: Students and healthcare workers were recruited from educational institutes and retail pharmacies/health facilities, respectively, located in a purposively selected sub-city of Addis Ababa. A questionnaire was designed to assess tramadol use and abuse using informed and consented students, pharmacy professionals working in medicines retails outlet, health professionals working in clinics and regulatory professionals working in the regulatory arena. Descriptive statistics were coded and analyzed using simple excel spreadsheet and SPSS analysis was also used to predict use and abuse and need for regulation of Tramadol.

Results: About a quarter (24.3%) of adults and adolescents knew tramadol and 18.15% adults and adolescents used tramadol. From tramadol users, 11.76% used to get happiness and for recreation. All dispensers knew tramadol was not an OTC and 87.5% said they didn't dispense it without prescription. All the participants said there were certain age groups that misuse Tramadol. From those who used ever, 95.77% adults and adolescents get Tramadol from pharmacies and 4.23% from clinics.

Conclusion: School age groups abuse Tramadol for recreational purpose or to get happiness. All dispensers knew that school age group abuse tramadol, but the practice of dispensers did not correlate with their knowledge on tramadol abuse, as some of them were dispensing the medicine without prescription. Prescriber's knowledge on tramadol abuse was not as that of dispensers, some of them had no knowledge as it was abused. Therefore, regulatory body should intervene and strictly regulate the distribution and dispensing practice of Tramadol as a substance of abuse.

Keywords: Tramadol, substance use, Abuse, young Adults, Adolescents, Addis Ababa.

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Abbreviations and Acronyms

AAFMHACA- Addis Ababa Food, Medicine and Health care Administration and Control Authority

BMI – Body Mass Index

CPP- Conditioned Place Preference

DUDIT- Drug Use Disorders Identification Test

EFDA- Ethiopian Food and Drug Administration

FDA-US- Food and Drug Administration of the United States

FMOH- Federal Ministry of Health

MOR- μ-Opoid Receptor

ODT- O-desmethyl Tramadol

OR – Odds Ratio

OTC- Over the Counter

RADARS- Researched Abuse, Diversion, and Addiction-Related Surveillance

SPSS – Statistics Package for Social Sciences

WHO- World Health Organization

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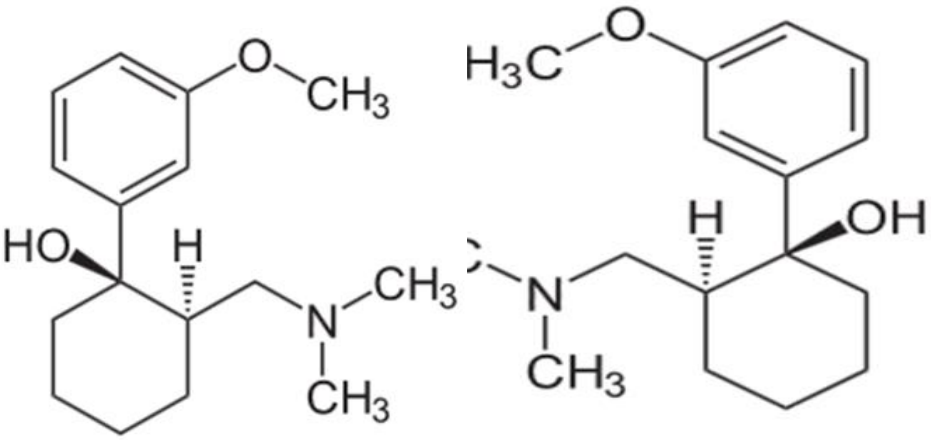
1. INTRODUCTION

1.1. Background

Tramadol is a centrally acting analgesic with a multimode of action and structurally related to codeine and morphine (WHO, 2014). Tramadol has a very good analgesic activity by its action on the central nervous system. It acts by various pathways such as a μ-opioid receptors (MOR) agonist or as a serotonin and norepinephrine reuptake inhibitor (H. Zhang, 2013). Tramadol alone as treatment option does not usually provide adequate analgesia. In chronic non-cancer pain, there is little evidence for the use of tramadol for more than three months (WHO, 2014).

Tramadol shares structural resemblance with codeine. Both tramadol and codeine have a 3-methoxy group on the phenyl ring and share O-demethylation as a metabolic step, producing metabolites with stronger μ-opioid agonist activity than the parent compound. In addition, the dimethyl amino-methyl moiety of tramadol contains the methylated ring nitrogen of morphine and codeine in its structure and forms an essential part that interacts with the μ-opioid receptor and monoamine transporters (Figure 1) (WHO, 2014).



(1S, 2S)-tramadol (1R, 2R)-tramadol

Figure 1: Structure of the enantiomers of Tramadol

More than 90% of its active ingredient is absorbed following oral, rectal and intramuscular (IM) administration. Tramadol is rapidly distributed in the body and its plasma protein binding is 20%. It has about 70% bioavailability, regardless of current food intake. Peak plasma concentrations will reach 1-2 h, 3 h and 45 min following oral, rectal and IM administration, respectively (WHO, 2014).

Tramadol is mainly metabolized by O- and N-demethylation as well as by conjugation reactions forming glucuronides and sulfates. In the body, tramadol is metabolized into a number of different molecules, the most important of which is O-desmethyl tramadol. This metabolite binds much more strongly to the MOR than tramadol does, making it more potent than the parent compound. So, tramadol is really a pro-drug, a molecule that is converted by the body's metabolism into the pharmacologically active drug (Subedi, et al, 2018).

Tramadol and its metabolites are mainly excreted via the kidneys. The mean elimination half-life is about 6 h. The O-demethylation of tramadol to M1, the main active metabolite, is catalyzed by cytochrome P450 (CYP) 2D6, whereas N-demethylation to M2 is catalyzed by CYP2B6 and CYP3A4. The wide variability in the pharmacokinetic properties of tramadol can partly be ascribed to CYP polymorphism. O- and N-demethylation of tramadol as well as renal elimination are stereoselective (Grond, et.al, 2004).

Tramadol is a centrally acting analgesic with weak μ-opioid agonist properties and is a weak inhibitor of norepinephrine and serotonin reuptake (H. Zhang, 2013). The analgesic effect of tramadol involves the opioid, noradrenaline and serotonin neurotransmission receptor systems (H. Zhang, 2013). Tramadol has some affinity for the MOR, whereas the active metabolite, M1 has high relative intrinsic efficacy and greater affinity for the MOR. It is generally used to control moderate to severe pain and also has the ability to suppress withdrawal symptoms of opioids. It can produce euphoria due to its anti-depressant-like properties via the mono-aminergic system (Jalali and Thomas 2018).

M1's analgesic potency is claimed to be about one tenth of that of morphine. Tramadol is used to treat both acute and chronic pain of moderate to moderately severe intensity. M1 also shows analgesic action by acting as weak MOR agonist (Subedi, et, al, 2018).

The (+) enantiomer of tramadol acts as a MOR agonist as well as by inhibition of the reuptake of serotonin, whereas (-) enantiomer inhibits noradrenalin reuptake. Opioid receptors are G-protein coupled receptor and are of four types. Tramadol is the most used opioids analgesic act on MOR. The (+) Dextro enantiomer of tramadol shows MOR agonistic activity and enhances the activation of central dopamine (Subedi, et, al, 2018).

The fundamental purpose of medicine regulation is to protect public health and to ensure that medicines on national markets and in international commerce are safe, effective and of good quality, and used in accordance with good practices. Medicines are important aspects of public health and must be available and accessible to the public (WHO, 2016).

To improve access to medicines, good governance is crucial and contributes to health systems strengthening. Good governance in the pharmaceutical sector refers to the formulation and implementation of appropriate policies and procedures that ensure the effective, efficient and ethical management of medicine regulation, in a manner that is transparent, accountable and follows the rule of law (WHO, 2016).

Preclinical, clinical, and epidemiologic studies prior to 1994 suggested that tramadol has a low abuse potential, which led the Drug Abuse Advisory Committee to recommend to the US Food and Drug Administration (FDA) that tramadol be approved as a nonscheduled analgesic (Arend. et, al, 2011). However recent reports are indicting that tramadol could have an increased abuse potential, forcing regulatory authority to revise scheduling of tramadol (EFDA, 2021 report)

Tramadol has been marketed in Ethiopia in different dosage forms and strengths. Recently, it has become one of the most widely dispensed analgesics in many countries, including Ethiopia (EFDA, 2021 report).

1.2. Statement of the problem

Substance use is harmful leading to decreased academic performance and psychiatric disorders such as depression, lethargy, hopelessness, and insomnia (Friderichs, et al 2012). It also undermines economic and social development and contributes to crime, instability, and insecurity. Drug abuse is a major burden to society, causing economic, health, crime-related costs as well as losses in productivity (Murano .et, al 2010)

Many cases of dependence with tramadol have been described among individuals with a history of substance abuse. Physical dependence and withdrawal symptoms have also been described in long-term, infrequent users, who consume high doses of tramadol without a history of misuse of other substances and this behavior is thought to pose a clear risk of dependence. There is growing evidence that the development of physical dependence to tramadol is dose-related, and administration of supra-therapeutic doses lead to a similar dependence profile to morphine. Whereas the risk of physical dependence is lower than prototypic opioids when low-dose tramadol is used over an extended period (Lian et al.1999).

Dependent individuals, who appear to be adolescents, who consume supra-therapeutic amounts of the drug, display withdrawal symptoms. However, these are not exclusively related to its opioid effects and may reflect withdrawal from catecholamine and serotonin receptors. It is thus possible that acute dosing regimens are not sufficient to produce pronounced opioid-like effects but that a sustained high-dosing regimen of tramadol or its abuse results in the development of neural adaptations characteristic of dependence for other mu-agonists (Lian et al.1999).

Tramadol is considered to be safe and thought to have minimal potential for abuse. But still no adequate data exist on its dependence potential (Arend. et, al, 2011). Though tolerance and dependence were not described after repeated administration of tramadol in humans, case reports that tramadol can lead to dependence are emerging (Arend. et, al, 2011).

Students constitute a high risk group for engaging in a risky behavior such as, substance abuse there are several factors contribute to the initiation of substance abuse by students (Reifman A, 2003).

People use drugs for a variety of reasons, including boosting their confidence and self-esteem, ability to make sense of things, and overcome general feelings of inadequacy towards themselves or the world. Anecdotal reports show use of tramadol as recreational substance, suggesting that it is abused by young adults in Addis Ababa. However, there are no studies conducted to address this issue.

This study therefore sought to shed light on the issue so that the output could be used for regulatory decision. The findings are expected to inform regulatory decision-making, guide public health interventions, and raise awareness among healthcare providers about the prevalence of tramadol misuse. By shedding light on the extent and nature of tramadol abuse among young adults in Addis Ababa, this study aims to contribute to more effective prevention and control strategies for tramadol misuse.

1.3. Literature review

1.3.1. Therapeutic or Medical Use of Tramadol

Tramadol is a centrally acting analgesic with a multimode of action. It acts on serotonergic and noradrenergic nociception, while its metabolite O-desmethyl Tramadol acts on the μ-opioid receptor. Its analgesic potency is claimed to be about one tenth that of morphine. Tramadol is used to treat both acute and chronic pain of moderate to moderately severe intensity. Tramadol alone as treatment option does not usually provide adequate analgesia. In chronic non-cancer pain, there is little evidence for the use of tramadol for more than three months (WHO, 2014).

Tramadol is believed to be a relatively safe analgesic. The main adverse reactions to tramadol therapy are nausea, dizziness, and vomiting, especially at the beginning of the treatment. Even if tramadol does not cause clinically identified respiratory depression at normal dose for treatment, it is contraindicated in patients with diminished respiratory function (WHO, 2014).

Tramadol is used worldwide and is listed in many medical guidelines for pain treatment. It is mentioned as a step-2 analgesic in the WHO guidelines for cancer pain relief. Tramadol is also listed on several national essential medicines list. It is, however, not listed on the WHO Model List of Essential Medicines (WHO, 2014).

Tramadol, like other opioids, is commonly used for acute and chronic pain conditions. The scientific evidence is extensive, although mixed in terms of efficacy of the drug as an analgesic. Multiple systematic reviews suggest a role for tramadol in relief of various pain conditions including osteoarthritis, neuropathic pain, refractory restless leg syndrome, chronic low backache, and cancer pain (Roussin. et, al, 2015). Tramadol may be appropriate when non-opioid analgesics are ineffective or contra-indicated (Roussin. et, al, 2015).

1.3.2. Non-medical use, abuse and dependence potential

As animal studies showed tramadol causes physical dependence, but this is not truly seen in all studies. In monkeys, only mild to moderate withdrawal symptoms were detected (Friderichs et, al, 2012).

After a short period of tramadol's introduction in the US market, a post-marketing surveillance was carried out and the result showed that the reported rate of tramadol abuse was 1-3 cases per 100,000 patients in the first three years (1995-1998) (Jalali.et, al, 2015).

Analysis report of the surveillance data over five years (1995 to 2000) indicated an incidence of withdrawal symptoms of about 0.5-1 per 100,000 individuals, which peaked in 1996, that is, one year after its introduction in the USA. (Roussin. et, al, 2015). Further post-marketing surveillance up to 2004 showed that the rates of abuse remained the same, even though the new brands and new generic formulations were introduced in the US market (Silber. et, al). This study indicated that tramadol abuse was found almost exclusively (95%) in individuals with a history of other substance abuse. Based on this study, it was concluded that tramadol as therapeutic use of analgesics rarely leads to abuse in pain patients (WHO, 2014).

In a WHO committee study conducted in different countries, 25 respondents confirmed that there was recreational/harmful use of tramadol and 12 stated that there was no such use. The common routes of administration were reported as oral by 14, oral/injection by 5 and one each inhaling/sniffing, injection and oral/inhaling/sniffing. Common formulations of tramadol reported were tablet by 12, tablet and liquid forms by seven, and powder/tablet and powder/ tablet/ liquid one each. The reported use was by the general population in seven responses and in clubs in two responses. Five respondents reported that there were deaths related to tramadol use (WHO, 2014).

The study done in Egypt included 204 school students, out of which 148 (72.5%) were males, 106 (52%) secondary school students, and 114 (55.9%) from rural areas. The mean age was 15.26 ±1.59 years (range 13–18 years). As urine analysis indicated, among school students, 18 (8.8%) were using tramadol. From those who were using tramadol, 15 (83.3%) were using tramadol only, while three (16.7%) were using more than one drug with tramadol (cannabis, tobacco, or alcohol). Two-third of the school students started using tramadol with tobacco smoking, 22% started with cannabis and the remaining used more than one substance. Even if their urine screen indicates tramadol positive, six students denied that they were using tramadol, while 12 students admitted using tramadol use. Majority (75%) of the students used tramadol once a month, 8.3% used 2–4 times per month and 16.7% used more than 4 times per week. The starting age for smoking was 16.1 ±1.4 and for tramadol use was 16.5 ±1.1 (Medhat, et al, 2016).

The FDA Med Watch system concluded the abuse potential was as low as 1 to 3 cases per 100,000 patients during the first 3 years of tramadol marketing, and approximately 97% of those abusing tramadol had a history of other substance abuse (Epstein et, al, 2006). However, there were many case reports after initial marketing phase of tramadol abuse, which contradicts with the improvement of its safety potential (Zhang. et, al, 2012).

A study conducted in Guangzhou City, China, found that demographic factors such as age, education, marital status, ethnicity, and occupation did not significantly influence tramadol use patterns. Among the 23 participants, the median age was 23.4 ± 4.1 years (ranging from 18 to 34), with 73.9% under the age of 25. Most users (87.0%) had no prior history of drug abuse before tramadol use, and 90.0% used tramadol alone, while 10.0% used it in combination with other substances primarily cough syrup (5 subjects) and methamphetamine (3 subjects). The median dose was 750 mg per use, reaching up to 2000 mg at most, and the median duration of use was 61.8 ± 30.2 months (ranging from 5 to 112 months). The average age of first use was 18.3 ± 4.0 years, and all participants administered tramadol orally. The main reasons for use were peer influence (60.9%) and curiosity or the desire for stimulation (39.1%). Sources of tramadol included private clinics or pharmacies (12), normal pharmacies (6), and the illegal market (6). Additionally, around 70% of the participants had been admitted at least once for detoxification or drug reduction (Zhang & Liu, 2012).

A study done in Malmo, Sweden included 59 participants, 56 were male, and the mean age was 18.0 years (standard deviation 2.66 years, median 17 years, and inter-quartile range 16–20). The study was done by hair analysis of all participants and 19 (32%) specimens were positive for prescription opioids. From these, 18 (31%) patients were positive for tramadol, eleven specimens (19%) for cocaine, five (8%) for synthetic cannabinoids, one each for methadone and codeine and the rest for amphetamine and diazepam (Olsson et, al, 2017).

A study conducted at Hawassa University found that 10.9% of tramadol abusers used the drug for recreational purposes, while 8.7% reported using it to relieve stress or frustration, or to enhance physical performance (Adanech Shiferaw, 2024).

In a study conducted in Lebanon, 52.9% of pharmacists demonstrated good knowledge regarding the use and abuse of tramadol, whereas 47.1% exhibited poor understanding of tramadol abuse (Farah Tarhini et al., 2020). Similarly, a study from Saudi Arabia reported that 76.75% of

pharmacy professionals possessed knowledge about tramadol use and misuse (Alshayban et al., 2019).

Furthermore, a study at Menoufia University in Egypt revealed that 33.2% of students were engaged in tramadol abuse (Abdelfattah et al., 2019) and the study done in Iran indicated 4.71% of students had a history of tramadol abuse (Pourmohammadi et al. 2019).

1.3.3. Problems related to Tramadol use

Using tramadol for a long period of time may cause physical dependence. It may also cause addiction. Therefore, stopping and reducing the dose may precipitate withdrawal symptoms (Subedi, et al, 2019). In the USA, an estimated 1.6 to 1.8 million Americans reported misuses of tramadol from 2015 to 2017 (Reines, et, al, 2020). From 162 patients who had bought tramadol from a medicine retail outlet in Iran, 92 (56%) came to pharmacy without prescription. About 103 (64%) patients met the criteria for addiction and got high when they used and unable to stop taking the drug. In total, 145 (89%) patients were aged younger than 30 years. Most of the patients with no prescription (88%) had abuse/addiction criteria (Zabihi. et al, 2011).

Tramadol abuse can easily lead to addiction. If someone shows the following behaviours, s/he may be dependent or addicted to it.

- ✓ Using the medication in a manner not prescribed
- ✓ Taking more of the medication than prescribed
- ✓ Reporting lost medication in order to obtain more
- ✓ Asking for refills long before refills would be due
- ✓ Using several doctors and pharmacies to get more Tramadol
- ✓ Stealing the drug or asking others who take the drug for a few pills

Thinking about or obsessing over when the next dose can be obtained or taken (Michael's House. 2022, March 5)

Tramadol abuse and addiction can cause many negative physical and psychological side effects. Many of the side effects of tramadol's addiction mimic those of opioid abuse and lead to depression. (MentalHelp.net. 2022, March 5).

1.3.4. Tramadol regulation

Tramadol was originally approved as non-controlled drug. However, currently, tramadol is a controlled drug in Bahrain, Australia, Iran, Mauritius, Sweden, Egypt, Saudi Arabia, Jordan, United Arab Emirates, Ukraine, and Bolivarian Republic of Venezuela etc. In the US, tramadol is listed in controlled substance class IV. In China, Tramadol is listed as "second category psychoactive substance." In the UK, tramadol falls under controlled class C substance (Jalali and Thomas, 2018). The French network for evaluation and information do not categorize tramadol dependence as a major problem but indicates a potential need to respond to growing trends (WHO, 2018). The abuse trend has decreased in all these countries after implementing further regulations. The Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System in the US reported a decline in opioid prescription drug and abuse, including tramadol due to higher regulatory measures (WHO, 2018).

In East African countries such as Kenya and Tanzania, tramadol is not classified as a controlled drug, but it is regulated as a prescription-only medicine (www.kenyalaw.org) and (tanzlii.org).

In contrast, Ethiopia has taken a more stringent regulatory approach in recent years. Although tramadol was not classified as a controlled substance at the time the data for this study was collected, it has since been placed under national control measures due to rising concerns about its misuse, particularly among youth and young adults.

The Ethiopian Food and Drug Authority (EFDA) reclassified tramadol as a controlled drug, which places additional legal and administrative restrictions on its manufacture, distribution, prescription, and dispensing. This reclassification reflects Ethiopia's growing recognition of tramadol's abuse potential and its commitment to preventing substance use disorders associated with this opioid analgesic (www.efda.gov.et).

1.4. Significance of the study

Tramadol addiction is a growing public health concern in Ethiopia, particularly among young people and adolescents. Despite being a prescription painkiller, its non-medical use has grown due to its perceived accessibility, affordability, and psychoactive properties. Therefore, the findings of this study will provide the regulatory authority with evidence of tramadol use and abuse so that the authority could make an appropriated decision about the status of the drug.

1.5. Research Questions

- Are there an abuse/ misuse of tramadol?
- Is tramadol abused by adolescents and young adults?
- What is the prevalence of tramadol abuse among adolescent and young adults?
- Do prescriber s and dispensers have awareness on tramadol abuse?
- Does the regulatory authority have awareness on tramadol abuse?

1.6. Conceptual framework

The rational use of medicine requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community. However, if patients or healthy person take medicines other than this, it is drug abuse. Thus, drugs that have a potential for abuse should be well regulated; otherwise, it could lead to substance abuse. The three parties that contribute to rational medicine use are prescribers, dispensers and users (Figure 2). These three parties should, therefore, appropriately use the medicine. If medicine is abused or has a potential for abuse, it should be regulated strictly.

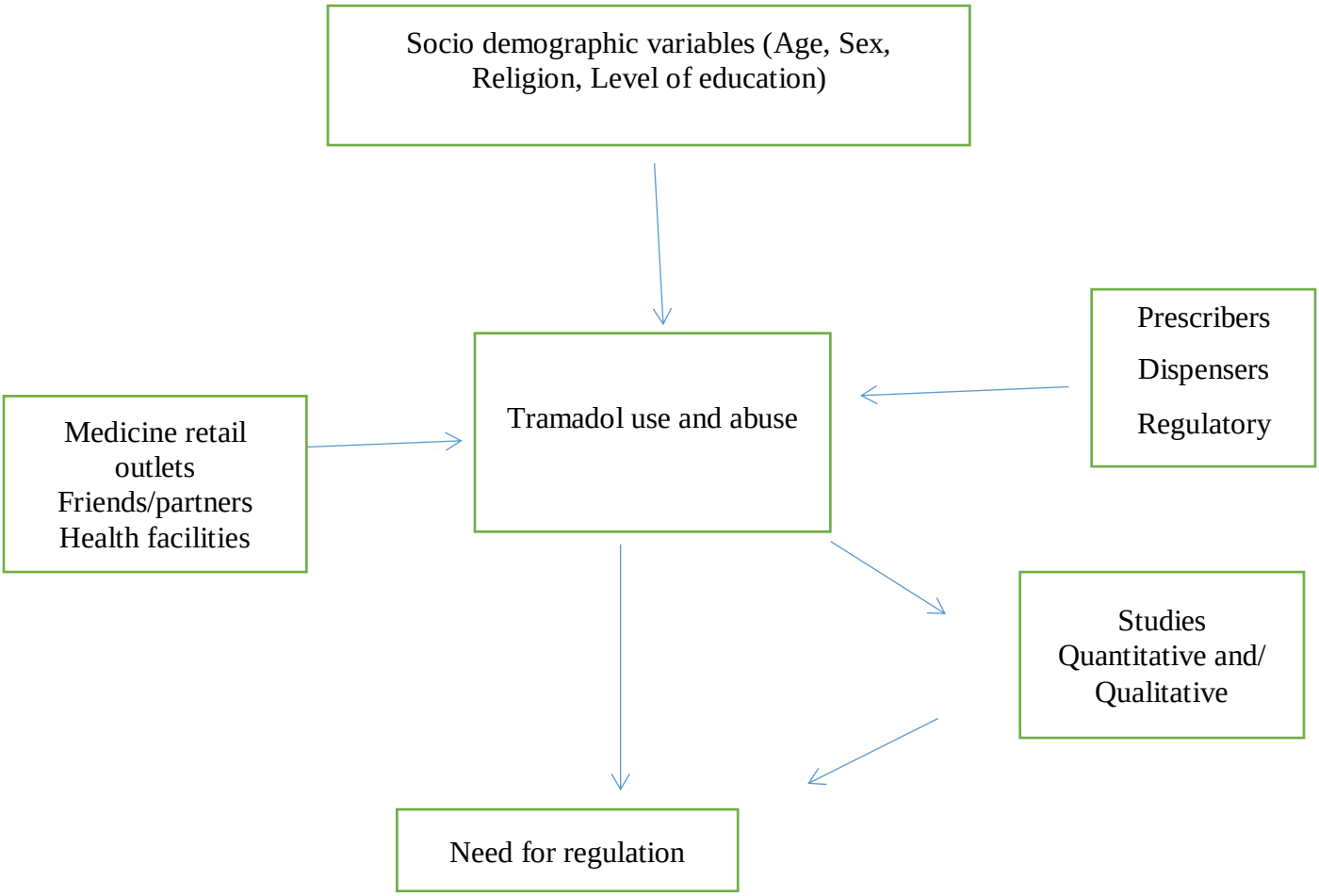


Figure 2: Conceptual framework of Tramadol use and abuse

2. OBJECTIVE OF THE STUDY

2.1. General Objective

The general objective of this study was to assess tramadol use, abuse and the need for its regulation in Addis Ababa, Ethiopia.

2.2. Specific Objectives

- To determine the prevalence of tramadol abuse among adolescents and young adults
- To assess awareness of the regulators about tramadol abuse
- To assess awareness of prescribers and dispensers about tramadol abuse
- To propose the regulatory legal framework for distribution and dispensing of tramadol

3. MATERIALS AND METHODS

3.1. Study design

Mixed method cross-sectional study designs were used. The study employed quantitative method to measure the prevalence of tramadol use. On the other hand, qualitative research method was used to explore which age groups come to health institutions and retail outlets without prescription for obtaining tramadol, and to assess the knowledge of health professionals on tramadol use and abuse.

3.2. Study areas and period

This study was conducted in public schools and youth centers in Bole sub city, Kirkos sub city and Lideta sub city, Addis Ababa, Ethiopia, from June 25th to September 15th, 2021. Addis Ababa is the capital city of Ethiopia. According to 2012 GC census, the population of Addis Ababa was 3.049 million. Out of which, 900,000 (30%) were within the age range of 15-30 years. Administratively, the city is divided into 11 sub-cities (Kolfe Keraniyo sub-city, Addis Ketema sub-city, Lideta sub-city, Nifas Silk Lafto sub-city, Akaki kality sub-city, Bole sub-city, Kirkos sub-city, Yeka sub-city, Arada sub-city, Gulele sub-city and Lemi kura sub-city) and 117 woredas. According to the master facility registry data(mfrv2.moh), there were 127 primary clinics, 596 medium clinics, 425 specialty clinics, 107 health centers, 35 hospitals, 60 medical centers, 882 pharmacies, 389 drug stores, and a total of 2621 health facilities in Addis Ababa.

3.3. Source and study population

All health professionals working in medicine retails outlets, health institutions, regulatory authorities, students and dwellers 14-29 years age of Addis Ababa formed the source population. All health professionals working in medicine retails outlets, health institutions, regulatory authorities in Addis Ababa as well as dwellers of age 14-29 years in Kirkos, Lideta and Bole sub cities that fulfill the inclusion criteria formed the study population.

3.4. Eligibility criteria

Adolescents and young adults 14-29 years of age who lived in Addis Ababa, health professionals involved in dispensing/prescribing tramadol and working in pharmacies /health institutions licensed from appropriate organization in Addis Ababa and those working in regulatory arena in

inspection directorate and narcotic and psychotropic substances (NPS) regulation team were included in the study. All medicines retail outlets below pharmacy level, health institutions that give secondary and tertiary health services and adolescents and young adults that were new for the city and did not live in Addis Ababa were excluded.

3.5. Sample size determination

Sample size was calculated by using standard a single proportion formula for cross-sectional studies as shown below.

$n = \frac{(Z\ \alpha/2)^2 \times P\ (1-p)}{d^2} = 384$ n= required sample size, Z= Z $\alpha/2$-score (1.96 for 95% confidence)

d= margin of error ± 5%, p= estimated proportion

$n = \frac{(1.96)2x0.5(1-0.5)}{(0.05)2} = 384$

Calculation was done using a 95% confidence level and margin of error of ± 5%, (50% was used for P, as there were no similar studies done in the country or in the region). Substituting these values into the formula gave a sample size of 384 and a contingency of 10% for non-response rate was added, giving a final sample size of 422.

3.6. Sampling procedures

Since this study focused on adolescent and adults, they are homogenous population. Purposive sampling was used to recruit study participants (Table 1). The sampling was performed at different levels. Initially, three sub cities were selected from the 11 ones based on the number of recreational areas where young adults misuse/abuse substances. Accordingly, Bole, Lideta and Kirkos sub-cities were selected. Three woredas that harbor the known recreational areas were then selected from each sub-city. To select medicine retail outlets, clinics and regulatory authority, non-probability sampling, which was purposive sampling, was used. Key informant peoples were selected and interviewed until the information obtained was saturated.

3.7. Data collection and management

3.7.1. Instruments

Data were collected using quantitative and qualitative questionnaires designed by consulting the literature. The questionnaires consisted of socio-demographic information, medical history, and tramadol use and treatment duration as well as the knowledge, attitude, and practice of tramadol misuse/abuse.

Data were collected by the principal investigator and trained school clinic professionals following a visit to facilities using the formal letter written to that concerned bodies.

Qualitative data were collected from three different population, dispensers, prescribers, and regulatory professionals, using a pre-prepared guide. Data were collected from 16 community pharmacies 11 clinics and 8 regulatory professionals.

3.7.2. Data quality control

To assure quality of the data, the following measures were undertaken; data were collected by the principal investigator, with some assistance from school clinic representatives. Pre-test was conducted to check the suitability of the data collection instruments. Based on the findings, necessary amendments were made on tramadol use part.

3.8. Study Variables

3.8.1. Dependent Variable

Tramadol use and abuse

- Recreational and use for happiness

3.8.2. Independent Variable

- Socio demographic variables (Age, Weight, Sex, Occupation, Religion, Level of education)
- Starting dose of Tramadol
- Duration of therapy
- Treatment with Tramadol

- Concomitant drug use
- Source of tramadol
- Age when start using
- Plan to stop using

3.9. Data analysis procedures

Data were entered into IBM SPSS version 21 for analysis. Descriptive statistics were computed to get summary results and binary logistic regression analysis was performed to predict factors which affect dependent variables at 95% confidence interval (95% CI). The association between tramadol use, abuse and need for regulation and explanatory variables was considered as statistically significant if a p-value was less than 0.05 in the linear analysis.

3.10. Ethical considerations

Before the study began, ethical clearance was obtained from IRB of the School of Pharmacy (Ref. No ERB/SOP/278/13/2021). Official letter was written by the School of Pharmacy, College of Health Sciences, Addis Ababa University to the retail outlets, health institutions, education institutions, and youth centers and regulatory authority seeking permission to conduct the study. Participants were informed about the objective of the study and their right to withdraw from the study at any time. Following the briefing, a verbal consent was obtained from each participant. Confidentiality and anonymity were maintained by removing all potential identifiers (names and mobile number) from the format and restricting data access, respectively.

3.11. Dissemination plan

The findings of this study will be submitted to and presented to the School of Pharmacy, College of Health Sciences, Addis Ababa University. It will also be submitted to Ethiopian Food and Drug Authority. Finally, efforts will be made to publish the findings in a peer reviewed scientific journal to make it publicly available.

3.12. Definition of Concepts

3.12.1. Definition of key terms

Medicines Use- means that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.

Medicine Abuse- is taking prescription drugs or OTCs with the sole intention of getting high.

Medicine Regulation- The process of testing, developing and marketing of medicines has to be regulated to protect the interests of the public and rational use.

Narcotic- a medicine subject to control in accordance with the convention issued by United Nation and ratified by Ethiopia and includes a drug that is categorized as narcotic drug by the EFDA.

Psychotropic substance- any substance subject to control in accordance with the convention issued by United Nation and ratified by Ethiopia and includes a drug that is categorized as narcotic drug by the EFDA.

Analgesics- Technically, the term analgesic refers to a medication that provides relief from pain without putting you to sleep or making you lose consciousness.

Adolescents- Age group 14-18 age

Young adults- Age groups 19-29

Prescribers - A physician or other health professional that is authorized by the appropriate organ to examine and diagnose human disease and treat by drug.

Dispensers- are health professional who is authorized by the appropriate organ that focus on the safe and effective use of medications which are qualified to dispense medications as well as giving advice.

Controlled substance- is substances that are controlled under the Controlled Substances Act (CSA).

Non-controlled medicines- medications prescribed to treat medical conditions that are not subject to some limitations as controlled substance prescriptions.

Over the counter – is medicines that somebody can buy without a prescription.

Nonmedical use - is the use of prescription drugs, whether obtained by prescription or otherwise, other than in the manner, for the reasons, or time period prescribed or by a person for whom the drug was not prescribed.

Dependence- defined as prescription medicines that have a recognized therapeutic need but also a higher potential for abuse.

Recreational use - defines as use of a tramadol for pleasure or enjoyment.

Use for happiness - refers to taking a tramadol for the intention of improving mood, feeling good, or escaping negative emotions.

Non-medical use - refers to using tramadol without health professional's prescription or for purposes other than treating a diagnosed medical condition.

Tramadol misuse - means using tramadol for not intended use or not recommended use.

4. RESULTS

4.1. Socio-Demographic Characteristics

From the three high schools and three youth centers, 422 students and adults were contacted, and from these 391(92.6%) students and adults responded to the study or questionnaires (130 females and 261 males). The socio demographic characteristics of participants are depicted in Table 1. The age group of the respondents were 209 (53.45%) for 14-18, 164 (41.94%) for 19-24, and 18 (4.6%) for 25-29 years.

Table 1: Socio-demographic characteristics of study participants in Addis Ababa city administration, Ethiopia September 2021(n=391)

Variable	Category	Frequency	Percentage (%)
Age	14-18	209	53.5
	19-24	164	41.9
	25-29	18	4.6
Sex	Female	130	33.2
	Male	261	66.8
Level of Education	High school	347	88.7
	Diploma	28	7.2
	Degree	16	4.1

4.2. Substance use characteristics

In this study, while most of the respondents have no history of substance abuse (70.8%) but there was a notable subgroup engaged in substance use (29.2%). Khat was the most used substance by 104 participants (26.6%), cigarettes by 34 participants (8.7%), and both by 24 participants (6.14%) (Table.2). Duration of use was one year for 55 (14.1%), 17 (4.3%) for two years, 34 (8.7%) for three years, 2 (0.5%) for four years, 11 (2.8%) for five years, and 4 (1%) for six years or more. About 10% (40) of the participants stated that if they had not taken these substances, they would have experienced some issues like uneasiness. Out of the total participants, 346 (88.5%) used painkillers and 188 (48.1%) of them did so without a prescription, and some of them (29, 7.4%) took the medicines daily.

Table 2: Distribution of respondents by substance use characteristics in Addis Ababa city administration, Ethiopia September 2021 (n=391)

Variable (N=391)	Category	Frequency	Percent
History of substance abuse	No	277	70.8
	Yes	114	29.2
Which substance do you use?	No	253	64.7
	Khat	104	26.6
	Cigarette	34	8.7
Ever had problem at work area	No	351	89.8
	Yes	40	10.2
Ever uncomfortable socially without taking substance	No	268	68.5
	Yes	123	31.5
Trouble remembering things if you do not take the substance	No	287	73.4
	Yes	104	26.6
Ever taken drug for pain relief	No	45	11.5
	Yes	346	88.5
Was it by prescription or OTC?	No	203	51.9
	Yes	188	48.1
Do you use every day?	No	362	92.6
	Yes	29	7.4
Do you know tramadol	No	296	75.7
	Yes	95	24.3
Ever taken tramadol	No	320	81.8
	Yes	71	18.2
Was it OTC?	No	364	93.1
	Yes	27	6.1

4.3. Awareness about tramadol use and abuse characteristics

Out of the 391 participants, 95 respondents (24.3%) reported that they were familiar with tramadol (Figure 3). As regards to gender, the proportion of the male gender was higher both in terms of knowing (75, 79%) and using (58, 81.69%) tramadol than the female gender (Figure 4). Disaggregating the data by age group revealed that 30 (31.58%) from 14-18, 60 (63.16%) from 19-24, and 5 (5.26%) from 25-29 knew tramadol (Figure 5). The proportion of participants who got information from health professionals and friends was 5.6% (22) and 18.7% (73), respectively.

A total of 71 (18.2%) of the participants used tramadol at least once and the majority (42.25%) belong to the age category of 14-18 years.

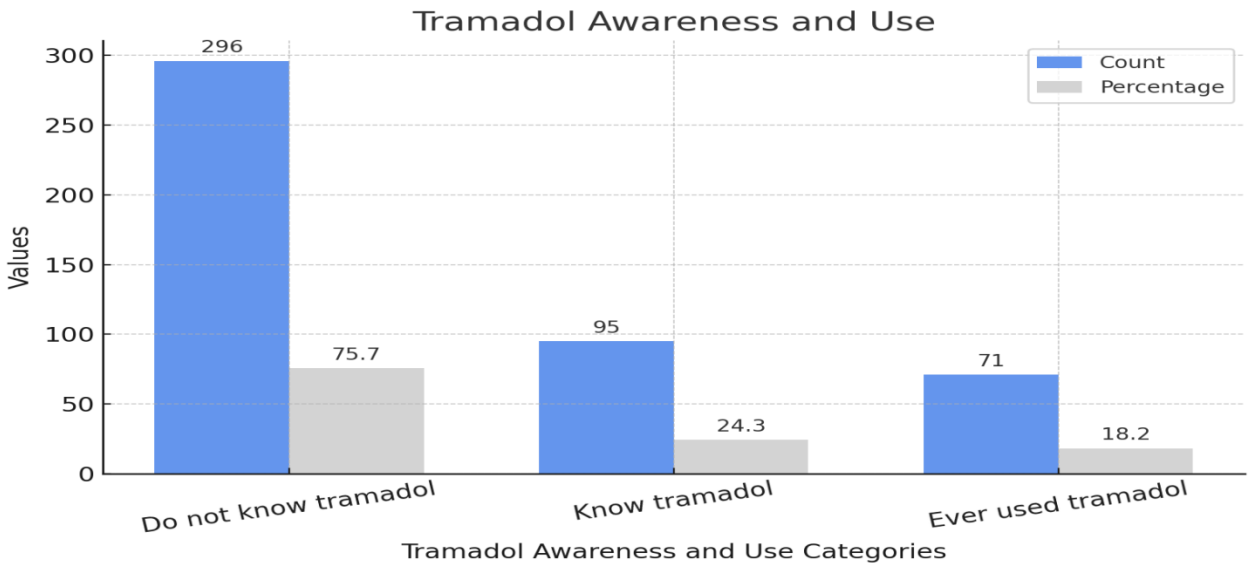


Figure 3: Distribution of respondents of Tramadol use characteristics in Addis Ababa city administration, Ethiopia September 2021(n=391)

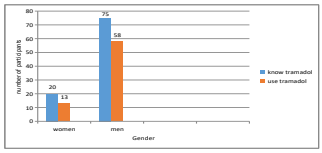


Figure 4: Distribution of participants that knew and used Tramadol by gender category in Addis Ababa city administration, Ethiopia September 2021 (n=95)

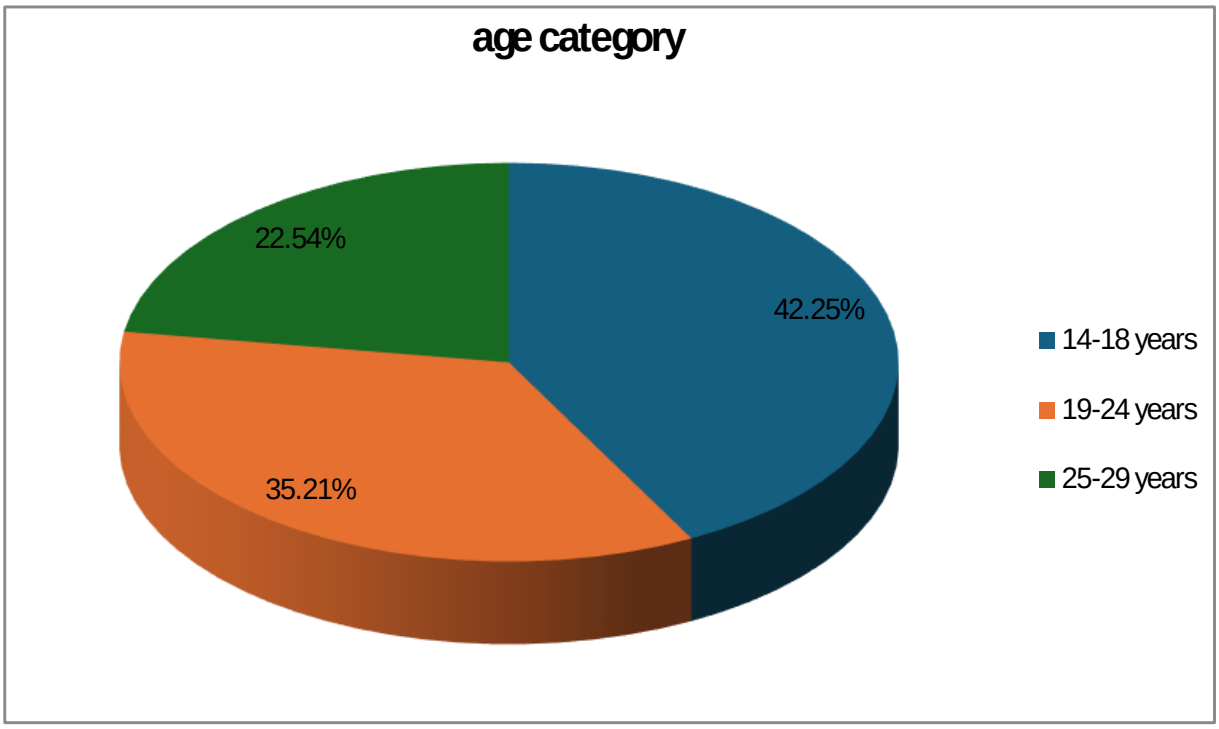


Figure 5: Distribution of Tramadol users by age category, Ethiopia September 2021 (n=71)

Among the study participants who used tramadol, 25 (35.21%) responded that it was prescribed for them by health professionals for treatment of different pain managements. The rest, however, did use it 46 (64.8%) for recreational and happiness purposes (Table 3).

Out of the participants who ever used tramadol, 30 (42.25%) used it once per month, 23 (32.40%) twice per month, and 18 (25.35%) three times or more per month. Majority of the study participants (68, 95.77%) reported obtaining tramadol from neighborhood pharmacies, while the remaining participants said they did get it from clinics. Only three (4.23%) of them used the injection form, whereas the vast majority (68, 95.77%) used tablet formulations (Table 3).

Table 3: Source of Tramadol and purpose they use in Addis Ababa city administration, Ethiopia September 2021 (n=71)

Variables	Frequency	Percentage
Source of Tramadol		
Pharmacy	68	95.77
Clinics	3	4.23
Purpose of use		
Recreational	30	42.25
Pain management	25	36.62
Happiness	16	21.13
Age When Started Using Tramadol		
14-18	58	81.75
19-24	6	8.45
25-29	7	9.8
Dosage Form of Tramadol Used		
Capsule/ tablet	68	95.77
Injection	3	4.23
Plan to stop using Tramadol		
No	22	30.98
Yes	49	69.02

Of the study participants who use tramadol, 49 (69.01%) had plans to cease using it, while 22 users said they had no plans to do so.

Reason for Tramadol use and related cause

According to the study, out of the 71 tramadol users, 46 used it for recreational purposes and 25 used it to treat pain (Table 6). The key factor influencing tramadol use was age (Figure 6), with users between the ages of 14 and 18 using the drug mostly and most frequently for recreational purposes. Majority of tramadol users (46 out of 71 or 65% of total) use for recreational and happiness, indicating a prevalent pattern of misuse.

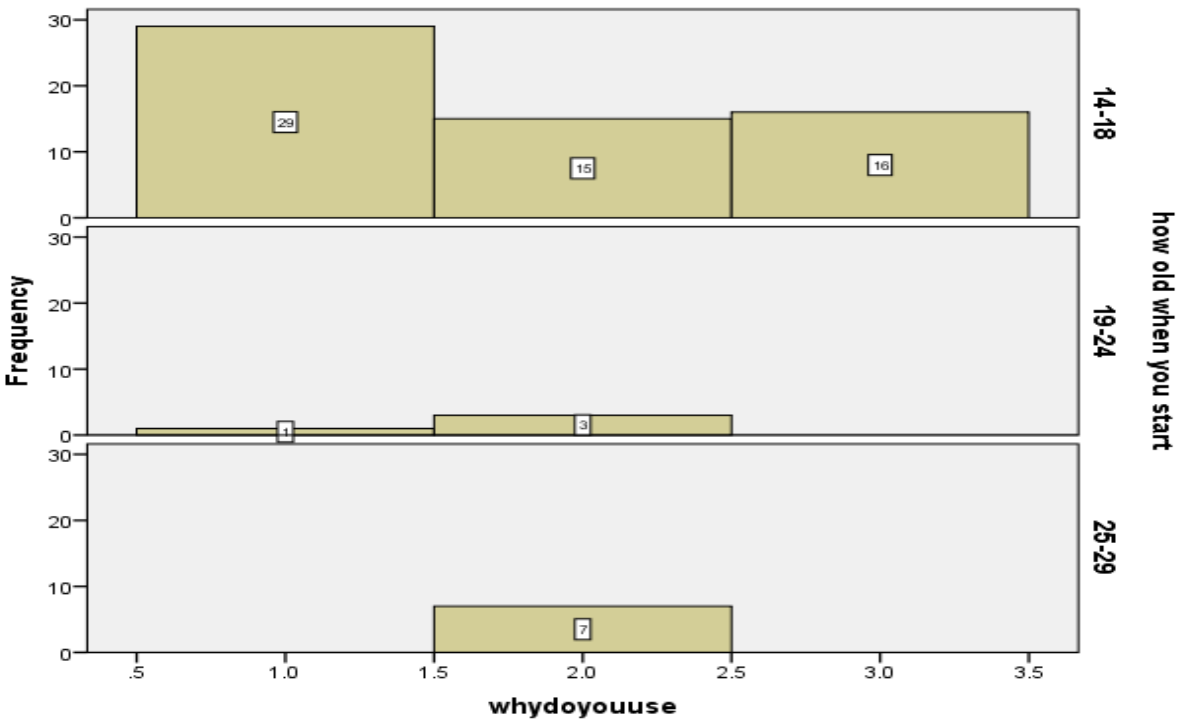


Figure 6: Reason for Tramadol use and age of users: the first bar represents recreation, the second pain management, and the third happiness, September 2021.

According to Figure 7, the age group between 14 and 18 use it for recreation than for treatment, suggesting that tramadol usage is influenced by age.

Effects of variables on Tramadol use for non-medical

The analysis of recreational tramadol use among participants revealed several significant associations with socio-demographic and behavioural factors. Age was a critical determinant; individuals aged 14–18 and 19–24 had significantly higher odds of engaging in recreational tramadol use compared to those aged 25–29. Both age groups showed a crude odds ratio (COR) of 2.43 (95% CI: 1.28–4.59), with p-values <0.001 and 0.005, respectively, indicating strong statistical significance. Regarding sex, males were more likely than females to report recreational use, with a COR of 1.31 (95% CI: 0.66–2.57), though this finding was not statistically significant ($p = 0.445$).

Educational status showed a marked relationship with recreational use. High school-level participants were significantly more likely to engage in recreational use compared to those with a

degree, with an exceptionally high COR of 19.324 (95% CI: 18.977–19.622, p = 0.037). In contrast, those with a diploma were less likely to use tramadol recreationally (COR = 0.11, 95% CI: 0.01–1.89, p = 0.037). A history of substance abuse was negatively associated with recreational tramadol use (COR = 0.39, 95% CI: 0.17–0.90, p = 0.027), suggesting that those with a history of substance use were less likely to report tramadol use for recreation.

When examining specific substances, khat use was significantly associated with higher odds of recreational tramadol use (COR = 2.80, 95% CI: 1.45–5.38, p = 0.007), while cigarette use did not show a significant association (p = 0.513). Awareness and prior exposure to tramadol were among the strongest predictors. Participants who knew about tramadol had an extremely high likelihood of recreational use (COR = 55.6, 95% CI: 13.4–230.2, p < 0.001), and those who had ever taken tramadol had similarly elevated odds (COR = 58.9, 95% CI: 22.97–151.1, p < 0.001).

Prescription status did not significantly influence recreational use (COR = 0.93, 95% CI: 0.27–3.23, p = 0.913). Age at initiation was another critical factor; those who started at ages 14–18 and 19–24 had significantly higher odds of recreational use compared to those who started at 25–29, with CORs of 22.28 (p = 0.003) and 20.10 (p = 0.003), respectively. Moreover, obtaining tramadol from a pharmacy was strongly associated with recreational use (COR = 20.6, 95% CI: 19.7–22.516, p < 0.001). As well as, intention to stop tramadol use showed a strong inverse association with recreational use. Those who reported plans to stop had significantly lower odds of continued recreational use (COR = 0.07, 95% CI: 0.04–0.15, p < 0.001), indicating a potential readiness for behaviour change among users. The regression analysis was depicted in table below, table 5.

Table 4: Logistic Regression of Factors Associated with Tramadol misuse, September 2021

Variables	Recreational use history		COR	p-value
	Yes	No		
Age				
14-18	17	192	2.43[1.28, 4.59]	<0.001
19-24	29	135	2.43 [1.28–4.59]	0.005
25-29	0	18	Ref	
Sex				
Male	33	228	1.31[0.66,2.57]	0.445
Female	13	117	Ref	
Education				
High school	46	301	19.324[18.977, 19.622]	0.037
Diploma	0	28	0.11 [0.01–1.89]	0.037
Degree	0	16	Ref	
History of substance abuse				
Yes	7	114	0.39 [0.17–0.90]	0.027
No	39	277	Ref	
Which substance				
khat	21	83	2.80 [1.45–5.38]	0.007
Cigarette	4	30	1.47 [0.46–4.65]	0.513
No	21	232	Ref	
Know tramadol				
Yes	46	49	55.6 [13.4–230.2]	<0.001
No	0	296	Ref	
Ever taken tramadol				

Yes	46	25	58.9 [22.97 – 151.1]	<0.001
No	25	320	Ref	
Was it prescribed				
Yes	27	44	0.93 [0.27, 3.23]	0.913
No	364	320	Ref	
How old when to start				
14-18	58	13	22.277[21.713, 42.406]	0.003
19-24	4	67	20.104 [0.000, 21.896]	0.003
25-29	7	304	Ref	
From pharmacy				
Yes	43	3	20.6 [19.7 – 22.516]	<0.001
No	25	320	Ref	
Plan to stop				
Yes	22	320	0.07 [0.04–0.15]	<0.001
No	24	25	Ref	

Factors Associated with Recreational Tramadol Use

According to the findings, tramadol use for recreation was highly related with some of socio-demographic and behavioral characteristics. Age was identified as a strong predictor (chi-square X2=7.68 and p=0.021), with younger people, notably teenagers and young adults aged 19 to 24 years, being more likely to use tramadol for recreational purposes.

Sex was also substantially related with recreational usage, with (chi-square X2 = 8.334 and p= 0.004) with males having a much greater incidence of non-medical tramadol use.

Educational status was also predictor of tramadol use for non-medical purpose. Individuals with lower levels of education, those still in high school, used tramadol recreationally, which was highly associated with chi-square X2 = 15.604 and p-value of 0.0 significance.

Another predictor of tramadol use for recreation was a history of previous substance use. Individuals with a background of using other substances were significantly more associated to engage in tramadol use recreational purpose with (chi-square X2= 9.662 at p=0.002) However, the specific type of substance previously used did not significantly predict whether an individual would use tramadol recreationally with (chi-square X2=1.293 and p-values of 0.524) indicating that it is the behavior of substance use itself, rather than the substance type, that contributes to non-medical use of tramadol.

In other way, there was no statistically significant association between tramadol use for recreational and either the user's intention to stop using or the source from which the drug was obtained did not associate with recreational use with (chi-square X^2 = 1.293 and p=0.524) and (X^2 =0.584 and p=0.445). This suggests that access alone does not fully explain the pattern of misuse.

One of the predictors identified was the prescription status of tramadol. The data clearly showed that recreational use was much more common among individuals who had no prescription for the drug. This indicates that access without prescription had associated with (chi-square X^2 =51.285 and p= 0.000) to tramadol misuse for recreational purposes. The summary of this was prepared in table below.

Table 6: Association between Recreational Use of Tramadol and Variables, Chi-Square Test September 2021, Addis Ababa, Ethiopia

Variable	Chi-square (χ^2)	p-value
Age	7.680	0.021
Sex	8.344	0.004
Level of education	15.604	0.000
History of substance abuse	9.662	0.002
Which substance used	1.293	0.524
Plan to stop	0.584	0.445
Source (from where you get it)	1.755	0.185
Was it prescribed for you?	51.285	0.000

4.4. Qualitative study

Table 07: Distribution of Study Participants by their Professional Role, September 2021, Addis Ababa, Ethiopia

Professional Job	Number of participants
Dispensers	16
Prescribers	11
Regulators	8

4.2.1 Dispensers' perspective on tramadol uses and abuse

All (16) of the pharmacists/dispensers were aware that tramadol requires a prescription and described the different brands that are sold there. Domadol 50 mg, Mabron 50 mg, Trama-denk effervescent, Tramadol 50 mg, Tramas 50 mg, Tramadol 50mg/ml injectable, and Mabron 100 mg/ 2 ml injections were the most popular products. All survey participants were aware of the pharmacological indications for tramadol, and 11 out of 16 (68.75%) of the dispensers claimed that tramadol is a fast-moving medicine. All community pharmacies received requests for oral capsules 50 mg on a regular basis most of which is without prescription. The majority of people who requested tramadol without prescription were school aged groups, and those who had prescriptions were those who had undergone trauma, had cancer, or were in extremely bad pain.

Even though all participants were aware of the issue, tramadol is a prescription-only medicine, 2 (12.5%) had the experience of dispensing it without prescription. They said that "*the customer would eventually get the medicine from other pharmacies, if we happen not to dispense it for them"*. Indeed, the investigator was able to buy the drug from three other pharmacies (not included in the study) without prescription.

All participants agreed that "*students and adult age group abuse tramadol for the purpose of feeling happy, to be alert, and for recreational purposes. The most common user age groups were 15-18 and 19-24 years and they use it to get high"*. All pharmacists who dispensed this medication, even those who did so without a prescription, claimed to warn patients about any potential negative effects when they dispense it. However, the investigator was not provided any

advice when he purchased the medication from the pharmacies, raising questions about the accuracy of this information.

A 35-year-old pharmacist claimed that "*a mother visited her drug store with numerous empty tramadol blisters and one containing the drug to inquire about the nature and uses of the drug. The mother informed the pharmacist that her son was a student and that she retrieved the blisters from the bottom of his bed after the pharmacist had described its use and indication*". The pharmacist added that *"many students beg for tramadol at her store in order to obtain it without a prescription"*. Additionally she said that, *"some students claimed that they would be unable to attend class if they failed to take the drug"*.

During the conversation, another pharmacist offered his experiences. He used to dispense tramadol without a prescription since he was unaware that students abused the drug. He now learned and stopped doing so. According to all of the pharmacists who were contacted, there are individuals who frequently purchase it with a prescription because they suffer from chronic pain as well as an adult age group who abuses it. Nowadays, there are people who misuse tramadol and use it in a variety of ways and contexts. For instance, "*they crush the pill and consume it while blending it with food or beverages"*. "*They also inhale it in and they did this in an effort to quickly find happiness"*.

In general, all dispensers advised that tramadol should be strictly controlled as an addictive medication. Public awareness should be raised, especially among young people and health professionals. They suggested that all regulatory agencies, from the federal to the woreda level, that oversee retail pharmacies and healthcare facilities, should control all medicine retail outlets to prevent the sale of tramadol without a prescription. All medical personnel who prescribe and dispense drugs should act properly, and if necessary, they should be aware of tramadol's legitimate uses as well as its abuse. At the conclusion, everyone agreed that it need to be put on the list of prohibited substances.

4.2.2. Prescriber's perspective on Tramadol use and abuse

During the study, eleven prescribers were interviewed, and their qualification shows that 2 (18.18%) were General practitioners, 6 (54.54%) public health officers and 3 (27.28%) professional nurses.

Tramadol's pharmacological indications and side effects were all known to the prescribers, who mostly gave it to people who complained of acute pain from trauma or chronic pain. All prescribers' assumed tramadol was a prescription medication, and 7 (63.63%) of them were aware that students (adults and adolescents) abused it; the remaining 4 (36.37%) were unaware of this. They said "*Secondary school students, and people up to the age of 22 (63.63%) who abuse tramadol do so to get high or for enjoyment*", according to those who were aware of the abuse, and learned of it from their peers. They also responded that, *"people who use it frequently to control their pain also become dependent on it and keep using it"*.

The prescribers alluded to the fact that "*students and adults that abuse/misuse tramadol get it from community pharmacy without prescription"*. Therefore they recommended that, *"the regulatory authority should give attention to community pharmacies that dispense it without prescription"*. General recommendation given by the prescribers about its abuse was strong regulation should be necessary, training for prescribers and dispensers should be given, and the medicine should be listed as prescription only medicines or if necessary, as controlled substance. In addition, they recommended that there should supportive or rehabilitation program for those who became dependent on tramadol.

4.2.3. Regulatory professional's perspective on tramadol uses and abuse

In this qualitative study, eight regulatory professionals took part, including two pharmacists who identified as female and six pharmacists who identified as male. All the regulatory experts agreed that tramadol is misused, and they claimed that youth and adults abuse the drug to get high, feel good, stay awake, and/or for recreational purposes. The experts based their conclusions on audit inspections and complaints from professionals who operate in dispensaries. According to a regulatory expert from EFDA, who is a member of the controlled substance team, the authority has evaluated a descriptive report that suggests tramadol usage and misuse in Ethiopia.

A female professional working at one of medicine regulatory authority said that she knew the use of tramadol or its indication. She also knew tramadol was registered in Ethiopia. She had information about tramadol abuse by age group of 15-25 years adolescents and adults. She said, "*The reason why they abuse is mainly related to development of tolerance to the drug. After frequenting, prolonged tramadol use, many people develop tolerance and they had to take larger doses to feel the same effect. Along with tolerance, tramadol users may experience withdrawal*

symptoms when they stop using the drug. Tramadol withdrawal can cause irritability, depression, and flu-like symptoms therefore they did not want to quit it". *She recommended "tramadol to be considered as controlled substance and should not be dispensed without prescriptions in all pharmacies and health facilities*".

The other regulatory professional working in one of the selected sub-city FMHACA responded that he knew tramadol is a registered medicine in Ethiopia. He heard the information from his colleagues about tramadol misuse. As per his information, young age groups abuse it for the purpose of getting happiness and stimulation. He had no information whether the regulatory authority considered tramadol as substance of abuse. He said, "*in the future, the regulatory authority should give training for concerned body and decide on how to regulate it*". He recommended "*that pharmacies should not dispense tramadol without prescription"*.

Another regulatory expert claimed to be aware that tramadol is a recognized medication in Ethiopia. She was aware of its exploitation in Ethiopia. She was aware that most young people who take tramadol are students. She told that "*Tramadol was taken by students because it functions similarly to many antidepressants in that it raises serotonin and norepinephrine levels in the brain, which can result in feelings of euphoria and well-being*". These enjoyable side effects may help some people maintain a routine of ongoing tramadol use. She believed that the "*regulatory authorities did not view it as an addictive substance*". "*The regulatory body should impose strict regulations and raise public awareness of potential abuse and its negative effects*".

Pethidine, morphine, codeine, tramadol, and Diazepam were mentioned as substances that are abused in Ethiopia by a regulatory expert working in the EFDA exper with a master's degree and pharmacy background. Based on their propensity for abuse, regulatory authorities classify abused medications as either narcotics or psychotropic drugs. Tramadol was registered in Ethiopia; he was aware of this. Tramadol is abused by young people because it behaves like narcotic painkillers, and he was aware of this from information. As he learned from his coworkers, "*adult age groups also misuse it*". He claimed that based on the facts he had, *"tramadol was regarded as an addictive substance*". He proposed that the *"regulatory body classify it as an addictive substance"*.

The other four regulatory professionals from all level of regulatory authority, mentioned controlled substances. They said that "*the regulatory authority categorized abused medicines*

based on their abuse potential as narcotic and psychotropic substances". They knew that tramadol is registered in Ethiopia and available in Ethiopian market. They all were aware that the young abuse tramadol to get high, especially students. An EFDA expert replied that tramadol is abused in Ethiopia because of peer pressure, used as pain killer, to get happiness and recreational purposes. All of them said that "*tramadol should be considered as substance of abuse. Regulation of tramadol was similar to the others NPS drugs except that tramadol is prescribed on normal prescription, this may be to increase access of tramadol for patients with non-communicable disease and others*". To regulate tramadol, the regulatory authority should require a special import permit for it as one of the regulation mechanisms, conducting audit inspection regularly at facility level, and importers and health facilities must report regularly about their consumption (Quarterly report of Tramadol use). Previously, it was out of the list of controlled drugs in Ethiopia but now a days there were so many reports of abuse/misuse of tramadol. Therefore, the regulatory authority needs to consider categorizing it under the list of controlled drugs. The themes that are categorized from the qualitative analysis are depicted in Table

Table 08: Codes, categories, and themes as identified from the qualitative study, Addis Ababa, Ethiopia, September 2021 GC

s.no	Codes	Categories	Themes
1	Pain management Recreational School age groups for study To get high	School age group use it	Reason why Tramadol is fast moving
	Come without prescription Complain they cannot study if did not take it	Prescription only medicine	
2	Should be audited Should be dispensed by prescription only Should be regulated by different prescription paper Should be stored in locked cabinet Import permit should be renewed every three months	Should be controlled substance	Regulation and awareness
	Training for prescribers Training for dispensers Community awareness	Training and awareness	

5. DISCUSSION

This is the first study that attempted to assess the use and abuse of tramadol in Ethiopia. The study recruited adolescents and young adults; an age group believed to be intimately involved with the use tramadol.

The research found that 24.3% (95) of the participants in the quantitative study acknowledged that they were aware that tramadol is a drug used to treat pain as well as for enjoyment and happiness. It's important to note that 11.76% (46) of the individuals in this study used tramadol for non-medical purposes. This finding was lower than that of a study conducted at Menoufia University, where one third of the students were used tramadol for non-medical uses (Abdelfattah et al., 2019) but this study closely aligns with the study conducted in Iran which reported 12.5 % prevalence of tramadol abusers in college students (Bashirian et al, 2014). However, the finding of this study indicated higher prevalence compared to study done on school children in Iran. Which revealed tramadol abuse rate of 4.71% (Pourmohammadi et al. 2019)?

Out of 71 participants those who used tramadol for various purposes 46 (64.8%) were used recreationally or to achieve happiness, whereas 25 (35.2%) were used for pain relief and therapy. The findings of this study were significantly higher than a study conducted at Hawassa University in Ethiopia, which found that 31.2% of tramadol users use it for recreational, stress alleviation, and addiction craving purposes (Adanech Shiferaw, 2024).

From the data analyzed, the abuse rate (11.76%) of tramadol observed in the present study is comparable with the study done in Iran (12.5%) (Bashirian, et al. 2014). However, it was very high compared to the rate reported during the first 3 years of tramadol marketing, the abuse potential was as low as 1 to 3 cases per 100,000 patients, and approximately 97% of those abusing tramadol were found to have a history of substance abuse (Jalal and Thomas, 2017).

The study explored that 95.77% of tramadol users reported obtaining the tablet form from neighborhood pharmacies, whereas the remaining users claimed to have obtained the injection form from clinics. The result of this study was closely related to the study done in Iran which reported 96.1% used tablet form (Ibrahim et al. 2017). However, a study conducted in Hawassa, Ethiopia, found that only 36% of users utilized the tablet form (Adanech Shiferaw, 2024).

The result of this study shows 68(95.77%) of tramadol users got the drug from pharmacy and 3(4.23%) got from clinics. However, EFDA assessment reports indicated that tramadol can be found in vendor shops near schools, and some students even sell it to other students (EFDA assessment study, 2018).

This study indicated that individuals who chew khat or use cigarettes were more likely to abuse tramadol. The study conducted in Egypt also shows that 20% to 40% of adults and 83% of adolescents with drug use disorders were found to use tramadol (Bassiony et al, 2015) and the study done in Iran indicated that 97% of those abusing tramadol were found to have a history of substance abuse ((Jalali.et, al, 2015).

In this study, all dispensers 16(100%) indicated that Tramadol is abused by students aged 15 to 24 years old, and that both men and women use it recreationally or for happiness and this is higher than study done in Lebanon only 52.9% of pharmacy professionals believed that tramadol is abused and misused (Farah Tarhini et al 2020), this was higher than assessment done by EFDA, which revealed that only 40% of dispensers were aware that there are certain groups of people that abuse tramadol, some of whom are between the ages of 13 and 19, and that both men and women are involved in misuse (EFDA assessment study, 2018).

According to the data analyzed, 87.5% of dispensers did not dispense it without a prescription, while 12.5% did, which is higher than the study done in Saudi Arabia 76% of the pharmacy professionals did not dispense without prescription (Alshayban et al, 2019) and EFDA assessment study's estimate that 75% dispensers did not dispense without prescription while 25% of dispensers sell it over the counter (EFDA Tramadol assessment study, 2018).

Prescribers prescribed mostly for those who complain severe pain like trauma and chronic pain and also they know the side effect of Tramadol and they think it is prescription drug but secondary schools students and adults up to 22 age (63.63%; n=7 of 11) abuse Tramadol to get high or for happiness and those who used it for long time to manage pain also abuse it.

Prescribers complain that students and adults, those who abuse/misuse got it from community pharmacy without prescription. In the same way the study done in Iran indicates that clients who request Tramadol from pharmacies without prescription seem to have a high potential for drug abuse, in particular those who do not have prescriptions and a high prevalence of people under 18 years of age seeking Tramadol (Arend I, etal, 2011 GC).

All regulatory professionals claim that Tramadol is abused in Addis Abeba, particularly by young people in schools but a study done in china (Haoran Zhang and Zhimin Li, 2013) stated that tramadol have low potential for abuse and misuse and the regulatory categorized as substance of abuse category II and in the same way the study done in Thailand indicated that tramadol was classified as schedule V substance regulatory authority.

All dispensers, Regulatory professionals and prescribes recommended that tramadol should be classified as substance of abuse and awareness and training should be provided for health professionals and adults in the same way the study done in Lebanon professionals recommended that prescribers and dispensers should give awareness for tramadol users and ministry of health should track tramadol use by prescription only (Farah Tarhini et al, 2020).

6. STRENGTH AND LIMITATIONS OF THE STUDY

Strength of the study

The study used mixed design method, which helps to triangulate the findings of quantitative results by qualitative study. The study considered all parts that can contribute to this study to fill the gap.

Limitations of the study

The study depended on questionnaires for adults and adolescents but only urine analysis of participants tells us the real prevalence. Most of the regulatory professional's response depended on previous report done on Tramadol by EFDA. The condition in and around Addis Ababa may not reflect the national situation.

7. CONCLUSION

The study clearly shows that tramadol usage is prevalent in Addis Ababa with a frequency of 18.16% and a use for recreational purposes of 11.76%. The results also showed that people between the ages of 15 and 22 are the ones that abuse it the most. In addition, history of substance use was another factor contributing for tramadol abuse. Even though they were aware it was a prescription medication, community medicine retail outlets were the main supplier of tramadol. The absence of stringent regulation and lack of awareness among dispensers contributed to its abuse. Factors such as substance co-users like khat and cigarette further exacerbate this issue.

Tramadol was proposed to be added to the list of prohibited substances by regulatory authorities, however, they dispense it without prescription or standardized prescription. Adding tramadol in narcotic list by regulatory authority might not be enough to combat tramadol abuse. Thus, health professionals must be trained and awareness for young age groups and their families should be provided. Generally, stringent control of distribution and dispensing can serve as a critical step towards reducing tramadol misuse in Ethiopia.

8. RECOMMENDATIONS

It is creditable that the EFDA oversees the dispensing of tramadol by classifying it as a controlled substance and restricting its use to colored prescription papers. This regulatory measure plays a crucial role in minimizing misuse and ensuring that tramadol is prescribed and dispensed responsibly.

The EFDA/responsible regional regulatory bodies should conduct audit-based inspection of pharmacies and health facilities to prevent illegal dispensing and diversions.

It is recommended that EFDA should create traceability systems to track tramadol distribution and dispensing.

The EFDA should raise awareness in the community, particularly among young people or students and even families.

The EFDA should provide training on safe prescribing and dispensing, and the abuse potentials and risks associated with tramadol use.

Lastly, the data strongly support the EFDA's decision to classify tramadol as a prohibited substance to oversee the entire tramadol supply chain, including production, importation, distribution, because many young people abuse it, which could result in socio-economic catastrophes.

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