Original Research Article

Tramadol Abuse among University Students in Khartoum State, 2018

Abstract:

Introduction: Tramadol is an atypical opioid that binds to μ-opioid receptors on neurons. It has a bioavailability of 70% and undergoes extensive first-pass metabolism in the liver. In most countries, it is a prescription-only medicine. Tramadol abuse has increased recently in the last few years between private universities in Khartoum state, Sudan. Common adverse effects of opioids are nausea, vomiting, relaxation, itching, mental confusion, delirium, urinary retention, sweating.

Methodology: A study was conducted on 176 university students in Khartoum from August to September 2018. Ethical approval was obtained from SIU REC and permission from each academic institution. A questionnaire sheet was developed to collect data related to drug abuse among students, including sociodemographic data and knowledge about drug use without prescription. ~~The collected data were statistically analyzed using Statistical Package for the Social Science version 16 programs.~~

Results: A study of 176 university students found that most were male (79.5%) and female (20.5%), with an age range of 21-25%. Most were medical students, with a majority in engineering, literacy, and computing fields. Most were aware of tramadol's analgesic "pain killer" effect, but only 53.7%) knew its hallucinogenic effect. Most abusers used tramadol for less than a year, with most starting in university life. Most abusers consumed various doses, with most consuming daily. Adverse effects of tramadol included physical symptoms, psychological symptoms, and attempts at quitting. Reasons for failure to quit were mainly compliance.

Conclusion : Tramadol abuse is prevalent among medical students in Sudan, with cannabis being the most frequently used co-administration drug. Reasons for initiation include elation desire, avoidance of life conflicts, and curiosity.

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Keywords: Tramadol, Abuse, university student, Sudan

Introduction

Tramadol drug is considered as an atypical opioid acts by binding to μ-opioid receptors on neuronsthat modulate the monoaminergic system by inhibiting noradrenergic and serotoninergic reuptake. Tramadol is analgesic drug that acts on the central nervous system (CNS) by synthesis of codeine analog, with weak but selective Muopioid agonism.[1,2] The bioavailability of tramadol is 70%, it undergoes extensive first-pass metabolism in the liver, liver-mediated N- and O- demethylation and glucuronidation via CYP2D6 and CYP3A4. The analgesic effect begins within less than 1 hour (if orally administrated), peaks in 2-3 hours, and duration of action lasts to 6 hours. Tramadol can be administered orally, rectally, sustained released, and parentally (IV or IM).[2–4]The Drug Enforcement Administration (DEA) in U.S doesn't schedule tramadol as a controlled substance since 2015. Tramadol is under national control in many countries since (2000 in Bahrain and Mauritius), (2001 in Australia), (2007 in Iran), (2008 in Sweden, Bolivarian republic of Venezuela, Ukraine, Jordan and Saudi Arabia), and in Egypt since 2009.[5]Food and Drug Administration (FDA) in China in 2007 classified tramadol as a second category psychoactive substance.[6]Incidence of tramadol abuse noticed clearly to be increased recently in the last few years between private universities in Khartoum state, Sudan.[6] According to the World Report in Vienna 2016, it has been estimated that 1 in 20 adults, used at least one drug in 2014, with a high number of drug-related deaths worldwide (43 deaths per million people aged between 15-65)years old.[6]The legal status of tramadol differs between countries, however, in most countries "including Sudan", it is a prescription-only medicine.[5] In Sudan, tramadol is a legally registered medicine. It is only available in hospital pharmacies as 75-150mg tablets and it is never sold without a medical prescription. The prescription should be written on a headed paper from a hospital or a specialist clinic and should sign and stamped by a registered specialist. Tramadol is also available from drug dealers, the available dose sold on the street is a much higher dose, a minimum of 225mg. Tramadol is known by many names in Sudan, but it is widely called "Al-Kharsha" which means itching in Sudanese traditional language, which is also a common side effect of tramadol [6].Common adverse effects of opioids are nausea and vomiting, relaxation, itching, mental confusion, delirium, urinary retention, sweating. Respiratory depression, myoclonic jerks, and seizures are less common but might occur in excessive opioid intake "overdose".[7]Generally, tramadol is considered as a low potential drug for dependency.

Tramadol dependency is usually more vulnerable in people with no history of substance abuse.[5,6]If abusers became addictive for it, they may be subjected to painful withdrawal symptoms when there is any period of suspension, or missed dose or smaller amount if highly addictive. These withdrawal symptoms vary according to the duration of addiction dose and frequency of ingestion. Mild form of withdrawal symptoms is nausea, vomiting, diarrhea, headache, and sweating. The severe form of withdrawal symptoms might be seen in people taking excessive amounts of tramadol, overdosed people, or co-administration of other medications such as antidepressants. This may result to cause "serotonin syndrome" that usually occurs after abrupt cessation. Serotonin syndrome symptoms included nausea, vomiting, diarrhea, tachycardia, muscle aches, mental confusion, agitation, shivering, tremor, seizure, respiratory depression and coma.[4,8–13]Avoidance of these symptoms is one reason why people taking excessive amounts of tramadol might refuge to illegal actions like steeling to get tramadol, and try "doctor shopping" in hope to find another alternative sources to for the prescription.[14]Unfortunately, there is no published data on tramadol abuse among youth in Sudan although it is a universal phenomenon with significant impact on public health, communities, social wellbeing of their families and society.[15,16]University life is often the most stressful period while acquiring new attitudes, skills and way of thinking. This period of life is usually associated with certain behavioral features including increase desire of risk-taking, because the students are going through a new and completely different experience in life. They pass through a lot of physical and mental exhaustion, and psychological instability as it is the phase of self-development and independence to deal individually with society and community especially when they get affected by the direct impact of the surrounding community. This whole self-dependency makes them feel weak in many situations and refuge to help from some psychoactive drugs such as painkillers "tramadol". This high prevalence is mostly noted due to its wider availability on the street and with the cheapest price compared to other types of drugs.[15,17,18]The study aimed to assess the awareness of tramadol effect, identify the pattern of tramadol abuse among the abusers, determine the association of dependence (physical and psychological) with the dependency duration, and to identify the initiating reasons for tramadol abuse among university level students. We also described the physical and psychological side effects in addition to physical and psychological withdrawal symptoms and correlated them with duration of abuse and frequency.Tramadol and desmetramadol may be quantified in blood,

plasma or serum to monitor for abuse, confirm a diagnosis of poisoning or assist in the forensic investigation of a sudden death. Most commercial opiate immunoassay screening tests do not cross-react significantly with tramadol or its major metabolites, so chromatographic techniques must be used to detect and quantities these substances. The concentration of desmetramadol in the blood or plasma of a person who has taken tramadol is generally 10–20% those of the parent drug.[19, 20, 21]

Methodology

A cross-sectional study was conducted on 176 university students of both sexes from Khartoum state during the period from august to September 2018 . A total of 176 university students of both sexes were randomly chosen according to the type of education representing medicine, engineering, and literacy and computer studies faculties. Ethical approval was obtained from SIU REC and permission was obtained from the administration office in each academic institution. Verbal and written consent was obtained from each participant. Students were assured anonymity and confidentiality of the information collected.A questionnaire sheet was developed specifically to collect data related to this study from students to assess the knowledge, attitudes, and prevalence of drug abuse among students. It included sociodemographic data and student's knowledge about the use of drugs without prescription. Accordingly, the essential modifications were done, and the final form was developed. The collected data were statistically analyzed using Statistical Package for the Social Science version 16 programs and expressed in Tables 1-6 and Figures 1-9.

Results

Out of 176 questionnaires distributed, respondent rate was 100%. Sociodemographic characteristics of participants showed that (79.5%) were males and the remaining (20.5%) were females, with an age range between (21-25) years old by (58%). Nearly half of them (49.4%) were medical students and the rest in the field of engineering (37.5%), literacy field (5.7%), computing field (6.2%) and (1.1%) in other unnamed fields. Regarding their social status, (91.5%) of them were unmarried, (5.1%) were married, (1.7 %) were divorced and (1.7%)of the students were widowed. (Table 1)

Table.1: Background and sociodemographic characteristics of the students (n= 176)

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	Frequency	Percentage (%)
Age groups	**Frequency**	**Percentage (%)**
16-20	65	36.9
21-25	102	58
26-30	9	5.1
Gender		
Male	140	79.5
Female	36	20.5
Academic field		
Medical field	87	49.4
Engineering field	66	37.5
Literary field	10	5.7
Computing field	11	6.2
Others	2	1.1
Marital status		
Married	9	5.1
Single	161	91.5
Divorced	3	1.7
Widowed	3	1.7

Regarding general knowledge or awareness of the drug uses only (53.7%) of them were aware of its analgesic "pain killer" effect, (28.2%) were assuming that tramadol is a stimulant, (14.2%) had mentioned that they thought it was a hallucinogenic drug, and the surprising result was that (22.2%) didn't know the effect of tramadol. Fortunately, (81.3%) had agreed that tramadol abuse among university students was a public health problem and (65.9%) of the total participants were aware about the consequences of tramadol abuse. (Table2).

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Table.2: Awareness about tramadol (n=176)

Knowledge about tramadol		
Stimulant	40	28.2
Pain killer (Analgesic)	85	53.7
Hallucinogens' drug	25	14.2
Unknown	39	22.2
Tramadol as a public health problem		
Agreement	143	81.3
Unknown	27	15.3
Disagreement	6	8.8
Knowledge about consequences		
Yes	116	65.9
No	60	34.1
Knowledge about the dose at first attempt		
Yes	107	60.8
No	69	39.2

Most abusers were using tramadol for less than one year (31.2%) and (21%) were abusing for 1 to 2 years. (55.1%) had their first consumption during their university life, (34.1%) started since secondary school and (10.8%) started to abuse since elementary school.

The doses known to be taken by the consumers were (56 mg "1/4 tab", 112 mg "1/2 tab", 225 mg "one tab", 337 mg "one and half tab", 450 mg "two tabs", 675 mg "three tabs", and more dosage) at the first consumption (24.4%, 34.1%, 24.4%, 3.4%, 8, 6.2%, and 2.8%) respectively. The dosesconsumeat the present time (continuation dose) which is (13.6%, 11.4%, 23.3%, 7.4%, 15.9%, 6.2%, and 22.7%) respectively with the doses. (Table 3). Most of abusers (44.9%) were consuming the current dose daily, (26.1%) were consuming every two to three days, and the rest of abusers (13.1%, 6.8%, and 9%) were consuming weekly, every two weeks, and once a month, respectively. (Table 4).

Table.3: Poly-drug abuse (n=176)

	Frequency	**Percentage (%)**
Other forms of substance abuse		
Present	125	71
Not present	51	29

Table. 4: Pattern of tramadol abuse (n=176)

	Frequency	**Percentage (%)**

The duration		
Less than 1 years	55	31.2
1 to 2 years	37	21
2 to 3 years	30	17
3 to 4 years	20	11.4
4 to 5 years	14	8
More than 5 years	20	11.4
Educational level at first consumption		
Elementary level	19	10.8
Secondary level	60	34.1
University level	97	55.1
The dose at first consumption		
56 mg (1/4 tab)	43	24.4
112 mg (1/2 tab)	60	34.1
225 mg (one tab)	43	24.4
337 mg (one and half tab)	6	3.4
450 mg (two tabs)	14	8
675 mg (three tabs)	11	6.2
More	5	2.8
The dose consumed currently		
56 mg (1/4 tab)	24	13.6
112 mg (1/2 tab)	20	11.4
225 mg (one tab)	41	23.3
337 mg (one and half tab)	13	7.4
450 mg (two tabs)	28	15.9
675 mg (three tabs)	11	6.2
More	40	22.7
The consumption frequency		
Daily	79	44.9
Every two to three days	46	26.1
Weekly	23	13.1
Every two weeks	12	6.8
Once per month	16	9

Out of 176 (100%) abusers, 125 (71%) participants used other poly-substances such as cannabis, alcohol, clonazepam, and others (92.8%, 44.8%, 43.2%, and 36%) respectively; while the 29% used tramadol solely. Among the 125 abusers (71%), (63.2%) of them used these poly-substances before tramadol abuse and(64.8%) out of the (63.2%) quitted these poly-substances at a later stage. (Table3, Figures 1, 2, and 3). The main reasons for using tramadol was for relaxation,(50.6%). followed by escape from reality by (46%), and curiosity to try a new drug was the third common reason for initiation of use, (40.3%) (Figure 4).

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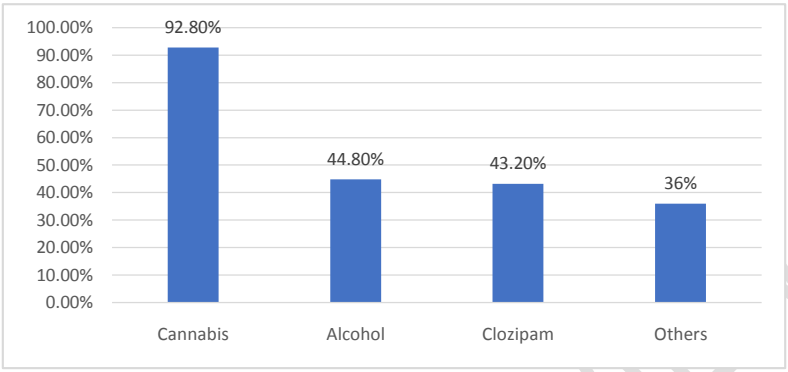

Fig.1: Types of substance abuse (n=125)

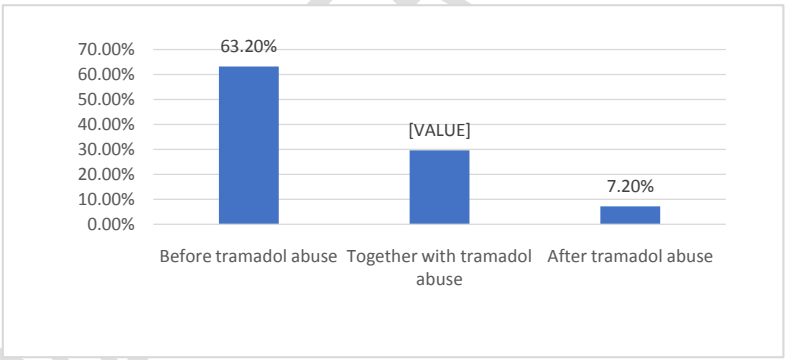

Fig.2: Tramadol abuse relation with other substance abuse (n=125)

Fig.3: Quitters from poly-drugs (n= 125)

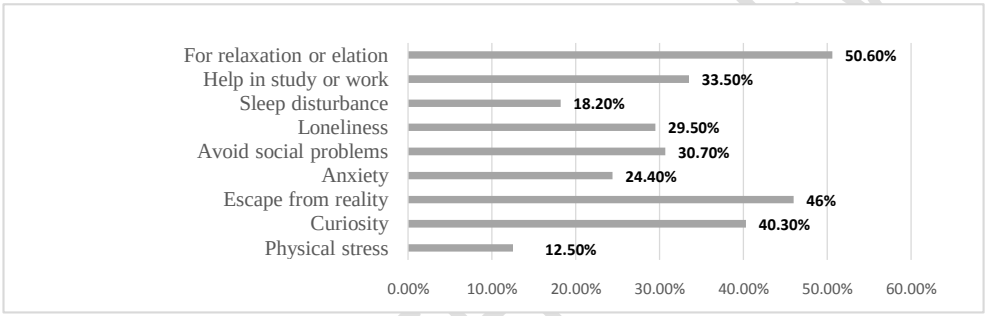

Fig. 4: Initiation of tramadol abuse (n=176)

We classified adverse effects of tramadol into physical and psychological symptoms, physical symptoms were sweating, itching, loss of appetite, loss of weight, nausea and vomiting, sleep disturbances, abnormal or involuntary movement, seizure, diarrhea, and constipation. The percentage of each was (62.5%,44.9%, 40.9%, 39.8%, 39.2%, 34.6%, 32.4%, 27.3%, 22.2%, 22.2%) respectively. Regarding the psychological symptoms (36.4%) of them preferred isolation, while (23%) of participants had suicidal thoughts and (20.6%) had an attempt at suicide. Others, (28.4%,39.8%) of them had an experience of anxiety and mood swing respectively. (Figure 5).

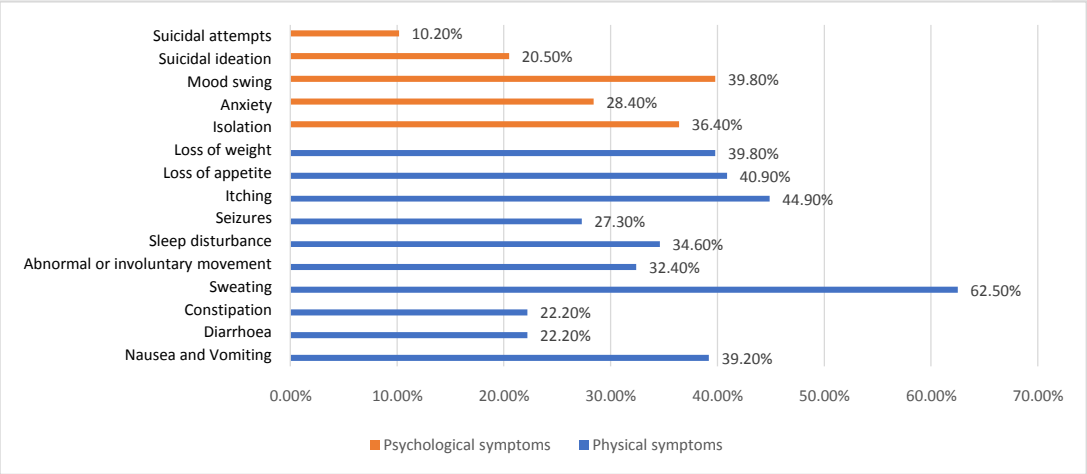

Fig.5: Physical and psychological side effects (n=176)

Among all abusers there was (71.6%) that had an attempt of quitting and (47.7%) of them sought help from different areas such as friends and relatives(52.4%); (15.5%) from family members; (14.3%) went to rehabilitation centers; (9.5%) went to a psychiatrist and psychologist; and (8.3%) sought help from other sources. Reasonsfor failure to quit from tramadol abuse were mainly failure to comply by most abusers (65.5%). (Table 5, figures 6, and 7).

Table .5: Quitting attempts of tramadol abuse (n=176)

	Frequency	**Percentage (%)**
Quitting attempt		
Yes	**126**	71.6
No	50	28.4

The most common withdrawal symptoms experienced by (71.6%) participants during the quitting attempts period were nausea and vomiting(54%);reported excessive sweating(31.7%);experienced body pain (muscles, joints, and bones)(56.3%);reported hallucination or delusions(29.3%);experienced loss of interest (anhedonia)(35.7%);had loss of appetite(36.5%);had loss of weight(34.1%);had abnormal or involuntary

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movements(30.9%);developed anxiety(30.9%); had sleep disturbances(50.7%);had mood swings (52.3%)suicidal thoughts (23%), and suicidal attempts (20.6%). (Table6, Figure8)

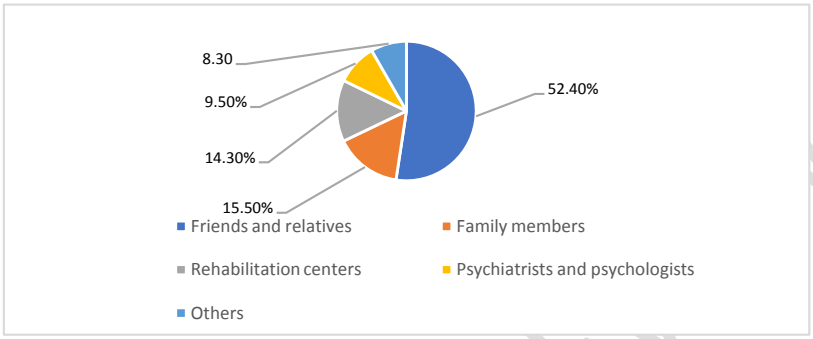

Fig. 6: People who were asked for help

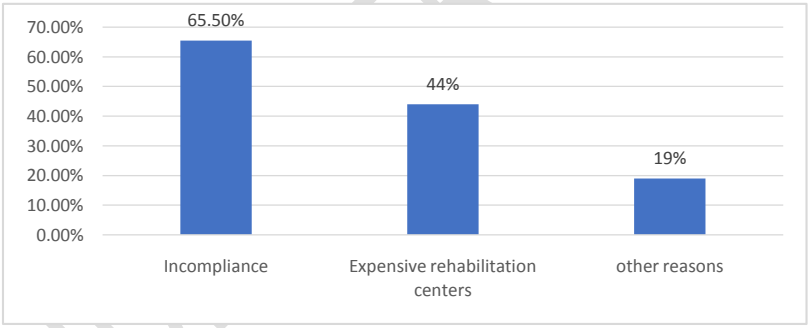

Fig.7: Reasons for failure to quit of tramadol abusing (n=84)

The source of tramadol as reported by participants was from various sources, mostly, direct from the drug dealers (64.2%), or from close friends (54%), and some of them (19.3%) from pharmacies. Unfortunately, (65.9%) of them commit illegal actions to get tramadol (Figure 8, table 6).

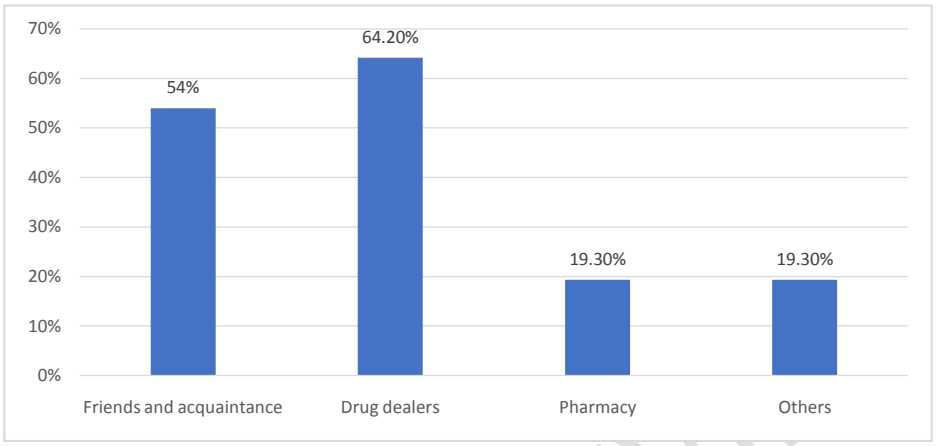

Fig.8: Sources of tramadol (n=176)

Table. 6: Illegal actions to get tramadol (n=176)

	Frequency	Percentage (%)
Illegal actions to get tramadol		
Yes	116	65.9
No	60	34.1

The results also revealed that (71.6%) of the abusers totally agree that tramadol abuse is a bad practice. (Figure 9).

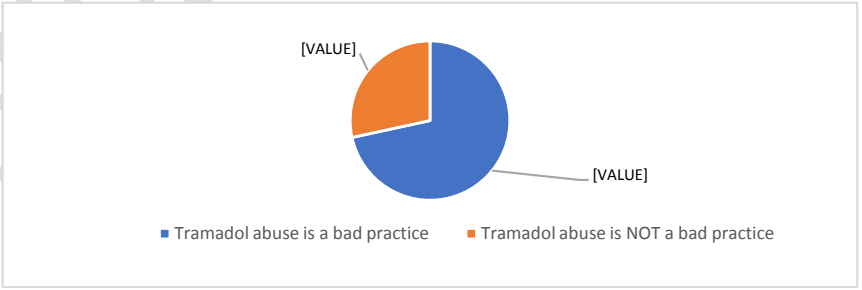

Fig.9: Insight about tramadol abuse as a bad practice (n=176)

Discussion

The study aimed to assess the awareness of tramadol effect, identify the pattern of tramadol abuse among the abusers, determine the association of dependence (physical and psychological) with the dependency duration, and to identify the initiating reasons for tramadol abuse among university level students.Most participants (58%) were within the age group (21-25)years, our age group compared to other studies shows that young adults are more prone than adolescences aged between (13-18) years[20], other reported retrospective study in north-eastern Nigeria with a higher percentage of abusers aged between (28-37) years[21] and a study done in the West of Iran and Western Region of Ghana showed similar results showed that the most frequent ages were between (21-25)years in both previous studies .[22,23]Comparing to those three different results the common age group included the adolescents in university level, this is most probably due to wide availability of the drug on the campus between students and drug dealers. It has been observed that most of the young age group are involved in drug abuse because it is the most vulnerable age for it, maybe because we share the similar culture and context,[24]whereas other age groups either to be too young to abuse or adult enough to seek such drugs.Considering gender proportion, (79.5%) of the study group are males, and (20.5%) are females, this shows that abuse of Tramadol is not limited to men only, but to ladies abusing Tramadol as well. Our result was nearly similar to that found in a recent study also in Nigeria (93.8%),[21,23] and most recent study in 2018 in the western region of Ghana, males percentage was (86%).[22]Tramadol abuse is predominant among males in Sudan as culturally is not acceptable for females to use drugs, for this reason, Males participants were more cooperative in filling out our questionnaires unlike females.The majority of participants in the present study were medical students (49.4%), the reason is due to that tramadol is highly restricted and there is a strong security deterrence forces against the abusers in the campus, that's why most of the cooperative participants were almost from medical field. Abuserswere unmarried were (91.5%), this is similar to the reported studies that Psychoactive substance use is a major problem among medical students, were most of them are singles "unmarried"[22,25], unmarried people with no responsibilities have more time for leisure and recreation in our context and culture.Only (29%) of participants were on Tramadol alone and (71%) were on poly drugs. The drugs most frequently used co-administration with Tramadol was cannabis (92.8%), then alcohol (44.8%), benzodiazepine (43.2%) and other drugs (36%). Most of poly drug abusers (63.2%) started abusing these drugs

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before tramadol abuse of whom (35.2%) reported that they quit these drugs because tramadol is an enough replacement. This result confirms studies in some cases reports were most of the cases had been in patients with a prior history of substance abuse[26], and in another case report study they found that rare cases of tramadol dependence have been described in patients without prior substance abuse history.[27]Poly medicate use frequently conveys more hazard than utilization of a solitary medication, because of an expansion in symptoms, and medication communications. The hazard level will rely upon the dose dimension of the two substances. This aggregate impact can prompt further unintended damage to wellbeing contingent upon what is as a rule perniciously included.Students in this study reported elation desire (50.6%) is the most common reason for initiation of tramadol abuse, avoidance of life conflicts (46%) and curiosity (40.3%) as the main reasons for initiation of tramadol abuse that is closely similar to previous study.[16] Other reasons reported in previous studies have included academic pressure, desire to improve academic performance (6.3%), to relax (29.9%), desire to experiment (33.1%), high social class (6.3%),to relieve stress (6.3%), to improve thinking and sharpness of mind (11.3%), to be accepted by others (5.5%), low self-esteem (3.2%), to remain awake at night (5.5%), to overcome boredom and tiredness (16.8%), to feel high spirit, to cope with problems (28.1%), poor relationship with parents (2.4%), family disputes (6.4%).[25,28–31]Adverse effects experienced as a result of using tramadol, showed thatmost participants were suffering mainly from excessive sweating (62.5%), loss of appetite (40.9%), itching (44.9%), loss of weight (39.8%), nausea and vomiting (39.2%), sleep disturbances (32.4%), abnormal or involuntary movement (32.4%), diarrhea (22.2%) constipation (22.2%), seizures (27.3%) which is mostly due to tramadol overdose or due to classical opioid withdrawal syndrome[21], isolation (36.4%), anxiety (28.4%) and mood swings (39.8%).These results are similar to previous studies about tramadol intoxication that confirm Tramadol overdose has been one of the most frequent causes of drug poisoning, especially in young adults with history of substance abuse and mental disorders. Nausea, vomiting, Central Nervous System (CNS) depression, tachycardia, and seizure are the most common findings in this kind of poisoning. Cardiopulmonary arrest was found as the cause of death in cases who had ingested more than 5000 mg tramadol.[9,11,13,32–35)]

Significant portion of participants (20.5%) have Suicidal thoughts and (10.2%) with actual attempt to commit suicide,that explains a similar results in previous study shows that the risk of suicide mortality is greater among individuals receiving higher doses of opioids(>100

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mg/day).[36] That is supports results in previous studies about association between tramadol intoxication and suicidal attempts.[13,37] Suicidal behavior is a significant problem for people with co-occurring disorders seeking addiction treatment.[38] This explains that tramadol addiction has a serious psychological impact because it frequently damages or destroys familial, professional, personal, and financial relationships, further increasing the risk of suicide. Thus, the role of psychological support is very necessary to be one of the essential parts of treatment under psychiatrists and psychologists, especially if it was in a well-developed constrictive and effective rehabilitation centers to deal with addicted people and to educate young students about the danger and consequences of tramadol abuse through lectures, workshops, organizations and media. In this study, (44%) of the participants failed to quit because they couldn't afford the cost of the rehabilitation centers, so we need to develop sponsored rehabilitation centers with free accessibility that offers the best program options and high facilities.Attempt to quit was reported by (71.6%) of participants, of them (100%) experienced withdrawal symptoms. Psychological symptoms are the most frequently reported like mood swings (52.3%), anxiety (30.9%), Sleep disturbance (50.7%), and hallucinations (29.3%) which are not normally observed in opiate withdrawal symptoms. Physical symptoms (56.3%) of these body pain (muscles, joints and bones) (40.3%), Nausea and vomiting (54%) are the most frequently reported.We studied the relation between physical and psychological dependency with the duration and frequency of consumption were there was a strong association between both physical and psychological dependency with the duration and there is only physical dependency with the frequency of consumption unlike the psychological dependence, Also, we tested the relation between physical and psychological withdrawal symptoms to survey the highest dependency rate, the result was close, but physical symptoms were more frequent). That is similar toprevious study reported in china 2013, it shows that tramadol with no history of substance abuse has a clear risk of producing high abuse potential under the long-term infrequent abuse and the high doses[39], also it is similar to new data have been reported and confirmed that tramadol dependence may occur when used daily for more than a few weeks.[5] Unfortunately, there is a wrong misconception among the abusers that tramadol has a low potential for dependency, this misconception could be a significant reason for initiation of abuse until it causes a high physical and psychological dependency when it becomes so difficult to quit then. Thus, we need to educate the society about the danger of tramadol abuse and its dependency risks.

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Similar to previous studies we found that sources of tramadol were varying between drug dealers which were the commonest source (64.2%) close friends (54%), and pharmacies (19.3%). Only one study in China reported that private clinics and pharmacies were the main source to get tramadol.[39]that is why only licensed pharmacies should be allowed for importing tramadol under formal drug prescription. Furthermore, legal bodies should enforce strict laws against drug dealers. Most of them (65.9%) engaged illegal actions to get tramadol[16,22], that's could be due to that student's expense is not sufficient enough to cover the price of the tablets he/she buy, especially when drug increasing in price every day, due to deteriorated economic situation in the country.

Conclusion

• Tramadol abuse is prevalent among males in Sudan due to cultural norms.

• Majority of participants were medical students (49.4%).

• Most abusers were unmarried (91.5%).

• Most frequently used co-administration with Tramadol was cannabis (92.8%), followed by alcohol (44.8%), benzodiazepine (43.2%), and other drugs (36%).

• Most poly drug abusers (63.2%) started abusing these drugs before tramadol abuse.

• Poly medicate use often conveys more hazard than single medication use due to expansion in symptoms and medication communications.

• Elation desire (50.6%), avoidance of life conflicts (46%), and curiosity (40.3%) were the main reasons for initiation of tramadol abuse.

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Refrances

1. Bravo L, Mico JA, Berrocoso E. Discovery and development of tramadol for the treatment of pain. Expert Opin Drug Discov. 2017 Dec;12(12):1281–91.
2. Kaye AD, Kaye AM, Urman RD. Essentials of pharmacology for anesthesia, pain medicine, and critical care. 1st ed. Kaye AD, Kaye AM, Urman RD, editors. Springer, New York, NY.

Springer, New York, NY; 2015. 904 p.

3. Tao Q, Stone DJ, Borenstein MR, Codd EE, Coogan TP, Desai-Krieger D, et al. Differential tramadol and O-desmethyl metabolite levels in brain vs. plasma of mice and rats administered tramadol hydrochloride orally. J Clin Pharm Ther. 2002 Apr;27(2):99–106.
4. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in Tramadol: Pharmacology, Metabolism, and Misuse. Anesth Analg. 2017 Jan;124(1):44–51.
5. WHO. WHO Expert Committee on Drug Dependence. Thirty-sixth report. World Health Organization technical report series. Switzerland; 2015.
6. 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 Res Int. 2013.
7. Pasero C, McCaffery M. Pain Assessment and Pharmacologic Management - E-Book [Internet]. Elsevier Health Sciences; 2010.
8. Sansone R a, Sansone L a. Tramadol: seizures, serotonin syndrome, and coadministered antidepressants. Psychiatry. 2009;6(4):17–21.
9. Lehmann KA. Tramadol for the management of acute pain. Drugs. 1994;47(1):19–32.
10. Tashakori A, Afshari R. Tramadol overdose as a cause of serotonin syndrome: A case series. Clin Toxicol. 2010;48(4):337–41.
11. Boyer EW, Shannon M. Current Concepts: The Serotonin Syndrome. N Engl J Med. 2005;352(11):1112–20.
12. K.A. M, J.A. A, T.E. A. Tramadol exposures reported to statewide poison control system. Ann Pharmacother. 2005;39(6):1039–44.
13. Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The hunter serotonin toxicity criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. QJM - Mon J Assoc Physicians. 2003;96(9):935–642.
14. Lehmann KA. Tramadol in acute pain. [French] Le tramadol dans les douleurs aigues. Drugs. 1997;53(2):25–33.
15. Osman T, Victor C, Abdulmoneim A, Mohammed H, Abdalla F, Ahmed A, et al. Epidemiology of Substance Use among University Students in Sudan. J Addict. 2016;2016:2476164.
16. A.B., Abiodun OA, Sajo S. Alcohol and psychoactive substance use among medical students

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of the University of Ilorin, Nigeria. Eur Sci Journal, ESJ. 2014;1(8):69–83.

17. Fawzi MM. Some medicolegal aspects concerning tramadol abuse: The new Middle East youth plague 2010. An Egyptian overview. Egypt J Forensic Sci. 2011;1(2):99–102.

18. Spear LP. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev. 2000 Jun;24(4):417–63.

19. Karhu D, El-Jammal A, Dupain T, Gaulin D, Bouchard S (2007). "Pharmacokinetics and dose proportionality of three Tramadol Contramid OAD tablet strengths". Biopharmaceutics & Drug Disposition. 28 (6): 323–30. .

20. 41. Tjäderborn M, Jönsson AK, Hägg S, Ahlner J (2007). "Fatal unintentional intoxications with tramadol during 1995–2005". Forensic Sci. Int. 173 (2–3): 107–11. doi:10.1016/j.forsciint.2007.02.007.

21. 42. Baselt, R. (2017) Disposition of Toxic Drugs and Chemicals in Man, 11th edition, Biomedical Publications, Seal Beach, CA, pp. 2185-2188, ISBN 978-0-692-77499-1.

22. 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. Am J Drug Alcohol Abuse. 2015;17(1):61–6.

23. Ibrahim AW, Yerima MM, Pindar SK, Onyencho VC, Ahmed HK, Machina BK, et al. Tramadol Abuse Among Patients Attending An Addiction Clinic in North-Eastern Nigeria: Outcome of a Four Year Retrospective Study. Adv Psychol Neurosci Spec Issue. 2017;2(2–1):31–7.

24. Elliason EK, Sandow B, Asechaab T, Kpangkpari S and AR. Abuse and Misuse of Tramadol among the Youth in the Wassa Amenfi West Municipality in the Western Region of Ghana. Psychol Psychol Res Int J. 2018;3(7).

25. Bashirian S, Barati M, Fathi Y. Prevalence and Factors Associated With Tramadol Abuse Among College Students in West of Iran: an Application of the Theory of Planned Behavior. Avicenna J Neuro Psych Physiol. 2014;1(1):26–30.

26. Males M. Does the adolescent brain make risk taking inevitable?: A skeptical appraisal. J Adolesc Res. 2009;

27. Babalola E, Akinhanmi A, Ogunwale A. Who guards the guards: Drug use pattern among medical students in a Nigerian University. Ann Med Health Sci Res. 2014;4(3):397–403.

28. Ojha R, Bhatia SC. Tramadol dependence in a patient with no previous substance history. Prim Care Companion J Clin Psychiatry. 2010;12(1):PCC.09100779.

UNDER PEER REVIEW

29. Pollice R, Casacchia M, Bianchini V, Mazza M, Conti CM, Roncone R. Severe tramadol addiction in a 61 year-old woman without a history of substance abuse. Vol. 21, International journal of immunopathology and pharmacology. England; 2008. p. 475–6.

30. Makanjuola AB, Daramola TO, Obembe AO. Psychoactive substance use among medical students in a Nigerian university. World Psychiatry. 2007 Jun;6(2):112–4.

31. Gebreslassie M, Feleke A, Melese T. Psychoactive substances use and associated factors among Axum university students, Axum Town, North Ethiopia. BMC Public Health. 2013;13(1):693.

32. Atwoli L, Mungla PA, Ndung'u MN, Kinoti KC, Ogot EM. Prevalence of substance use among college students in Eldoret, western Kenya. BMC Psychiatry. 2011;11(1):1.

33. Gupta S, Sarpal SS, Kumar D, Kaur T, Arora S. Prevalence, pattern and familial effects of substance use among the male college students-a north Indian study. J Clin Diagnostic Res. 2013;7(8):1632–6.

34. Shadnia S, Soltaninejad K, Heydari K, Sasanian G, Abdollahi M. Tramadol intoxication: A review of 114 cases. Hum Exp Toxicol. 2008;27(3):201–5.

35. Moulis F, Rousseau V, Abadie D, Masmoudi K, Micallef J, Vigier C, Pierre S, Dautriche A, Montastruc F MJ. Serious adverse drug reactions with tramadol reported to the French pharmacovigilance database between 2011 and 2015. Therapie. 2017;72(615–624).

36. Ahmadimanesh M, Shadnia S, Rouini MR, Sheikholeslami B, Ahsani Nasab S, Ghazi-Khansari M. Correlation between plasma concentrations of tramadol and its metabolites and the incidence of seizure in tramadol-intoxicated patients. Drug Metab Pers Ther. 2018 Jun;33(2):75–83.

37. Jovanović-Čupić V, Martinović Ž, Nešić N. Seizures associated with intoxication and abuse of tramadol. Clin Toxicol. 2006;44(2):143–6.

38. Ilgen MA, Bohnert ASB, Ganoczy D, Bair MJ, McCarthy JF, Blow FC. Opioid dose and risk of suicide. Pain. 2016 May;157(5):1079–84.

39. Hassanian-Moghaddam H, Farajidana H, Sarjami S, Owliaey H. Tramadol-induced apnea. Am J Emerg Med. 2013;31(1):26–31.

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