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First Generation Antihistamine, Irrational Uses and Risk of Dependence in University Of Khartoum Faculty of Medicine, 2018-2019

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Abstract

Background: The aim of this study is to investigate the prevalence of abuse, irrational use and dependence on antihistamine. This cross-sectional study, conducted during 11-months period. The study involve 388 students, participants were randomly selected from all levels. 57% of student use antihistamine without prescription, 17.7% of student use antihistamine for insomnia, 3.7% develop dependence; all of the student who participate use the drug without prescription and for insomnia. The cause of insomnia in 64.6% of student is studying anxiety and also there is correlation between using antihistamine for insomnia and level, age of student, abuse and dependence.

Keywords: Antihistamine, Irrational Uses, Abuse, Dependence

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Introduction

The effects of histamine on body tissues and organs can be diminished in four ways: inhibition of histamine synthesis, inhibition of histamine release from storage granules, blockade of histamine receptors, and physiological antagonism of histamine's effects. Of these approaches only the inhibition of histamine synthesis has not been employed clinically. H1-receptor antagonist is highly lipophilic and readily cross the blood brain barrier and interfere with the neurotransmission by histamine at central nervous system leads to drowsiness, sedation, somnolence, dizziness, tinnitus, anxiety, increase appetite headache, impairment of cognitive function memory and psychomotor performance the second generation is more lyophobic and less likely to cross the blood brain barrier. The first generation is uses for allergic diseases, coughs and cold and insomnia. They have been in clinical use since 1940s and 1950s they have poor receptor selectivity and often interact with receptor of other biologically active amine and causing ant muscarinic, antiadrenergic and antiserotonin effects.

Pharmacokinetics: First-generation antihistamines are well absorbed after oral administration, with peak blood levels occurring within 1 to 2 hours; the therapeutic effect usually lasts 4 to 6 hours, although some drugs are much longer acting. These antagonists are generally metabolized in the liver through hydroxylation. The metabolites and a small amount of parent compound are excreted in the urine (**Figure 1**).

Adverse Effects: Sedation is the most frequent adverse reaction.

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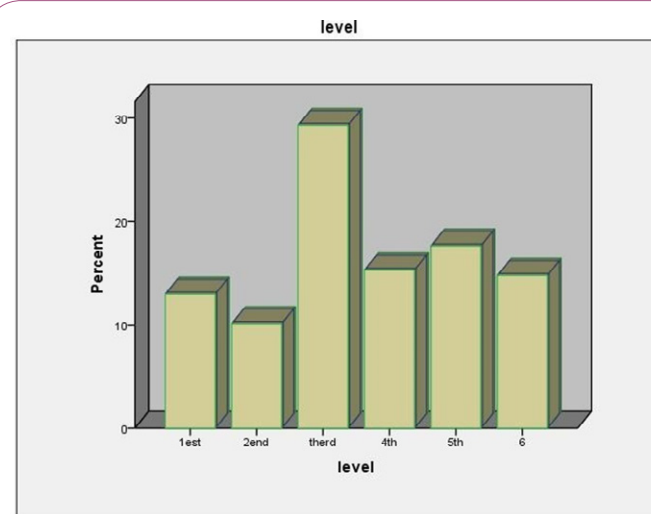


Figure 1 Percentage of the student according to their level.

An additive effect on alertness and motor skills will result if alcohol or an-other depressant is taken with these drugs. Anti- muscarinic effects caused by these drugs include dry mouth and respiratory passages, urinary retention, and dysuria. Nausea, vomiting,

constipation or diarrhea, dizziness, insomnia, nervousness, and fatigue also have been reported. Drug allergy, especially after topical application is fairly common. Tolerance to certain antihistamines may develop after prolonged administration. Teratogenicity effects of the piperazine antihistamines have been shown in animal studies [1].

Literature Review

Drug abuse

The vast majority of non-prescription drugs which are sold 'over-the-counter' (OTC) in pharmacies are used appropriately by patients. The term "abuse" is used to describe the use of drugs for non-medical purposes, for example, to experience their mind-altering effects. Products commonly recognized as having abuse potential include those which contain opioids, antihistamines, and laxatives. A study of abuse of non-prescription drugs was done by Glend in 1999 in Northern Ireland, to investigate the abuse of non-prescription (over-the-counter; OTC) products. A structured questionnaire covering various aspects of OTC drug abuse was mailed to all 509 community pharmacies in Northern Ireland. 253 responses were received (response rate 49.7%) after two mailings. Pharmacists named 112 OTC products they perceived were being abused in Northern Ireland. These were classified into 8 groups, with opioids, antihistamines and laxatives the most frequently reported. The frequency of abuse of all product groups was perceived to be either increasing or static. The number of clients suspected of abuse over a three-month period ranged from 0 to 700 (median=10, mode=6) with 55% being regular customers. Pharmacists employed several methods to limit patient access to products of abuse. The most common technique was to keep the product out of sight. Others included additional client questioning, providing advice and limiting the quantity of product sold. The majority of respondents agreed their role could be extended to include other methods of dealing with abusers, including participation in harm-reduction programmes to wean abusers off products. Geographical region and location of pharmacy were not significant factors in the abuse of OTC products. Research into methods of effectively dealing with OTC abuse is required and has commenced on the basis of these findings. Also in January 2008 James, E studied the abuse of prescription and over-the-counter medication and he found that diphenhydramine is mainly used as a sedative, hypnotic and antiemetic.

Drug used for self-medication must meet some safety criteria, and there are many studies accordingly, a cross-sectional study of knowledge, attitude and practice of self-medication among medical student currently studying first year was done in 2015 in Chitwan by Raj Kumar Mehta sujata Sharma. This study aimed to determine the knowledge, attitude and behavior of self-medical student, seventy five students were selected for the study using stratified random sampling technique and data was collected using semi-structured self-administered questionnaire. The study finding revealed, the mean age of 75 enrolled students was 20 years, 65.3% were in the age group of 17-20 years. Most of them were female (72%). Seventy three point three percent belong to urban area. Prevalence rate of self-medication of one year period

seems high i.e. 84% and 68.25% in were females.

The most common sources of information used by the respondent were pharmacist (60.31%) and text book (46.03%). More than half of the respondent found to have a good knowledge about self-medication regarding definition, adverse effect and different types of drug. The attitude was positive towards self-medication and favored self-medication saying that it was acceptable. This descriptive study has found that self-medication is very common among medical students, facilitated by the easy availability of drugs and information from textbook. Since inappropriate self-medication has the potential to cause serious harm, not only to students themselves but also to those whom they suggest medication. The respondent shows good knowledge towards self-medication and positive attitude towards self-medication favoring it is acceptable. Prevalence of self-medication was high due to minor illness. However, there is no significant association between prevalence and sex of respondents. Although the self-medication practice is inevitable; there is great responsibility of drug regulatory authorities and health care professional about the control of self-medication by explaining the students about total impact of drugs on the body. Another evaluation of abuse and dependence on drugs used for self-medication was done, but this time it was a pharmaco epidemiological cross-sectional study conducted during a 2-month period (from 15 January to 15 March 2007), relying on a questionnaire given to patients in community pharmacies in French in 2009 by Ludivine Orriols, to explore the feasibility of pharmacoepidemiological method to investigate abuse and dependence on drugs used for self-medication. Antihistamine was included in the study.

They designed a questionnaire to investigate pattern of drug use and harmful consequences of abuse. A total of 228 pharmacies were solicited: 167 from the network and 61 training course supervisors. The 228 solicited pharmacies represented 20.8% of the 1097 community pharmacies in the area. The main reasons for refusal to participate were as follows: constraint of staff time, some did not want to solicit their patients, and several pharmacies stated that they were not concerned by the problem of pharmaco-dependence. Where as 100 pharmacies originally agreed to participate, only 74 of the actively participated in the survey (32.5% of the pharmacies solicited initially). The number of pharmacies that actively participated in the study (n=74) represented 6.7% of the total number of community pharmacies in the Midi-Pyrénées area... Among the 74 pharmacies that participated in the study, 15 did not have the opportunity to include any patient according to the study protocol. They found that only one patient among 60 who had use an antihistamine drug use oxememazing to sleep, where-as this medicine should be used to treat cough, this result indicate that this method is reliable to obtain valuable information on the problematic use of drug obtained in pharmacy for self-medication [1]. Also a study in Jordan was done by Qutaiba Ahmed alkhemesaga in 2019, it was cross-sectional study, to investigate the prevalence of drug and non-medicine substances abuse and motivation factor among college student in Philadelphia University, the study involve 843 student, 531 male and 312 female they were selected randomly from different faculties. In this study, 93.00% of respondents were recorded to use at least one drug or non-

medical substance, 67.50% of all students were using drugs and 84.94% were using non-medical substance. The most commonly abused drug for sleep induction was the Antihistamines (Chlorpheniramine, Diphenhydramine and Chlorpheniramine), which were used by 60.11% of student. The study conclude that: Despite of controlled prescription of CNS effecting drug in JORDAN, there are many cases of such drug abuse between college students, prescription is require to prevent drug abuse, self- confidential and awareness courses for college student are essential to be one of the academic requirement in college stage [2].

Irrational use of drug

Histamine in the central nervous system plays an important role in regulation of sleep-wake cycle. In animals histamine activity has been shown to facilitate wake-fulness. Clinically histamine₁receptor antagonists are known to cause sedation and are often use for this purpose. According to irrational useof antihistamine a study ofdata in randomized double blind trials was done in 2012 by Joseph p, to evaluate the literature regarding the uses of antihistamine in the treatment ofinsomnia. Literature was identified via PubMed and Medline through April 1, 2012, using the search terms insomnia and sleep, each individually combined with histamine antagonist, tricyclic antidepressant, trazodone, mirtazapine, doxepin, amitriptyline, nortriptyline, trimipramine, doxylamine, diphenhydramine, and antihistamine. A total of 65 trials were evaluated and 16 met inclusion criteria. Data included randomized double- blind trials that statistically evaluated H1 receptor antagonist treatment in patients with insomnia compared with a placebo control or Food and Drug Administration–approved insomnia treatment. Trials selected evaluated sleep latency, wake after sleep onset, total sleep time, number of awakenings and/or sleep efficiency in a subjective or objective manner. A total of 65 trials were evaluated, and 16 met inclusion criteria. With the exception of low-dose doxepin, trials evaluating the clinical effectiveness of H1 receptor antagonists show mixed results and are limited by sample size and generalizability. Large, randomized, appropriately controlled trials are lacking, making it difficult to define the safety and efficacy of these agents. In contrast, low-dose doxepin has been shown to provide consistent sleep benefit compared with placebo. They concluded that Over-the-counter antihistamines may have a role for short-term insomnia treatment in younger adults, but tolerance develops rapidly. Mirtazapine should not be used solely for the treatment of insomnia. Sedating antidepressants can be considered after failure of first-line insomnia treatments. Patients taking these agents chronically should be evaluated for continued efficacy and potential harm. Low-dose doxepin may have a unique role in the treatment of insomnia in elderly patients given its tolerability, documented efficacy, and lack of important adverse effects [3]. On other hand cross-sectional investigation in French was done by Chuhsing kale Hsiao to investigate the prevalence of misuse, abuse and dependence on non-prescription psychoactive drugs. The study was in randomly solicited community pharmacies, an anonymous questionnaire was offered to adult.

A high prevalence of persistent daily user of sedative antihistamine

was observed where as these drugs are recommended only for short treatment courses of occasional insomnia, 75.2% of participants having taken doxylamine were daily user predominantly for more than six month.

The study conclude that as for hypnotic on prescription, persistent use of doxylamine for self-medication is not justified until an acceptable benefit-risk ratio for chronic sleep disturbances is shown by clinical data.

Also in 2009 a study was done in USA by Harold W Gosforth. The review seeks systematically to examine currently published data on the use of doxepin for the treatment of insomnia, and its pharmacological basis. Medline articles showing from a search of 'doxepin and insomnia' were included in the review.

They concluded that currently available data support the use of low-dose doxepin as preferential H1 antagonist for the treatment of primary insomnia. There are likely preferential effects upon sleep maintenance insomnia compared with sleep initiation given the role of histamine in the sleep–wake cycle.

Another cross-sectional study by S.S.A. SHAH, IN 3RD December 2015 and 19th august 2016 to quantify the number of allergic patients utilizing antihistamine with proper dose and to observe any side effects produced due to intake. A total of 200 purposive sampling from outdoor patient tertiary care hospital of Hyderabad, for a period of 6 months. Out of total 200 patients male was 68.5% and female was 31.5%). Maximum number of patients was from the age group between 16 – 30 years. Patients having flu were more in number of 34%, 31% were of common cold, 21% of skin rash & 12% were of cough. 37%. Loratidine was commonly used in patients which is 2nd generation H1 receptor antagonist (anti-histamine). 48% patients were taking BD dose, 41% of OD & 11% patients were taking TDS. Through the survey & pre-designed questionnaire, it was found that most of the patients were taking anti-histamine without the prescription of doctor as all anti-histamines are easily available in all pharmacies and the patients were experiencing side effects because of no dose adjustment by doctor or a pharmacist. 67% patients were experiencing Dry nose, 51% headache, 45% of dry mouth and drowsiness each, 42% were feeling sickness. It was concluded that patients are using antihistamine because of easy availability of the drug in pharmacy. Study analysis also shows that patient taking antihistamine for longer period of time due to lack of awareness. Frequently usage of antihistamine can cause drug dependence as well as adverse drug reaction.

Antihistamine dependence

The available literature has include dependence to diphenhydramine. There are also case report that have highlighted dependence to chlorpheniramine and promethazine depression has been the psychiatric disorder most commonly associated with antihistamine abuse in general. Across-section study was done by Anne Roussin in October 2013 in French, to investigate the prevalence of misuse, abuse, and dependence on non-prescription psychoactive drugs. 295 patients (mean age 48.5 years, 68.5% of women) having used one of the studied drugs during the previous month were included. A high prevalence of persistent daily users of sedative H1 antihistamines

was also observed. Where as these drugs are recommended only for short treatment courses of occasional insomnia, 72.2% of the participants having taken doxylamine (n=36) were daily users, predominantly for more than six months [4]. Also a hazards of antihistamine dependence was studied in a case report in psychiatric patients by Mukund G, in 26 march 2015, they present apatient with avoidance personality disorder, social phobia and dull normal intelligence, who presented with antihistamine dependence. In history he said that in order to calmhimself and get good sleep he began to regularly use pheniramine tablet since the past four years, initially start with a couple of tablets a day, the amount increased to 20 to 30 tablets a day since the past six months and now he present for treatment of anxiety and antihistamine dependence. This report highlights the need for vigilance regarding excessive use of OTC medication in patient with mental illnesses, as they can be used for persistent symptoms that don't respond to conventional treatment such as insomnia. In 1999 in New found land David. Reported three cases of chronic dimenhydrinate abuse, in two of the cases symptoms developed that suggested dimenhydrinate withdrawal syndrome, so he suspected that dimenhydrinate dependence may be much more widespread than is generally recognized.

Another case of antihistamine (pheniramine) dependence was reported in Istanbul, Turkey in December 2014 by Omer Saatci Oglu [5].

Materials and methods

Study design: This is descriptive cross sectional stratified sampling study.

Study area: The study was conducted in the faculty of medicine, university of Khartoum. It located in EL Qasr Ave, Faculty of medicine, Khartoum north, Khartoum state, Sudan. It is the oldest school of medicine in Sudan; will continue to play its leadership role as a world-class medical school model for newer and developing medical schools, in addition to its role on the regional & international scene. It is established in February 1924 as Kitchener medical school. In September 1951 the school was linked to Khartoum University College. After independence in 1956 Khartoum university college was upgraded to Khartoum university, the medical school became a faculty of medicine and started offering the MBBS degree. N.B University College was affiliated with university of London which awarded for the graduates its graduation certificate, and contribute in establish of the curriculum & exams regulation. The duration of teaching program is 6 years. The staff about 201 who teaches in 14 academic departments. The students' intake is about 350 students per year.

Study population: Medical students in university of Khartoum.

Sample size: Equation used: $n = N / 1+N (d)^2$

Where;

n: Sample size

N: Population size

D: Level of the precision

In this study N= 2434; d=0.05; So n = 344

Sample size was 388.

Variables:

The questionnaire consists of four parts:

- Demographics and insomnia assessment
- The irrational use of antihistamine in insomnia.
- The abuse of antihistamine.
- Dependence assessment.

Data collection tools

Data was collected through self-administered questionnaires.

Data collection methods

It was qualitative data collection using standardized closed-ended questionnaire and Google forms

Data management and statistical analysis

The data analyzed by chi-square test and correlation study was done using statistical package for social science.

Ethical consideration

Ethical approval from department of Community medicine, faculty of medicine university of Khartoum.

Consent is obtained from the doctor as written consent in the questionnaire. No information that can lead to identification of specific doctor will be taken.

Results

Socio-demographic Characteristics of the study population

The study include 388 participants, 79 male(20.6), 305 female (79.4). The age range was 15-30, 50 student (13%) in first year, 39(10.1%) in second, 113(29.3%) in third, 59(15.3%) 4th, 68 (17.6%) 5th and 57 (14.8%) in the 6th year, 268(70.2%) live with family, 114(29.8%) live in dorm (**Tables 1-12**).

Table 1 Difference in age of the students.

		Frequency	Valid Percent
Valid	15-20	187	49.2
	21-25	191	50.3
	26-30	2	.5
	Total	380	100
	Missing system	8	
Total		388	

Table 2 Prevalence of irrational use in abuse cases.

		Without prescription		Total
		Yes	No	
Do you use antihistamine in insomnia	Yes	59	4	63
	No	28	65	93
	Total	87	69	156

Table 3 Prevalence of dependence in abuse cases.

		Do you think you are depending on it		Total
		Yes	No	
Without prescription	Yes	5	71	76
	No	0	54	54
	Total	5	125	130

Table 4 Correlation between age and abuse.

		Age 1	Without prescription
Spearman's rho	Age1	Correlation Coefficient	1.000
		Sig. (2-tailed)	-
		N	380
Without prescription		Correlation Coefficient	-.152
		Sig. (2-tailed)	0.56
		N	158

Table 5 Correlation between sex and abuse.

		Sex	Without prescription
Spearman's rho	Sex	Correlation Coefficient	1.000
		Sig. (2-tailed)	-
		N	380
Without prescription		Correlation Coefficient	-.60
		Sig. (2-tailed)	0.454
		N	157

There is no significant correlation

Table 6 Correlation between level and abuse.

		Level	Without prescription
Spearman's rho	Level	Correlation Coefficient	1.000
		Sig. (2-tailed)	-
		N	386
Without prescription		Correlation Coefficient	-.204**
		Sig. (2-tailed)	0.010
		N	159

** . Correlation is significant at the 0.01 level (2-tailed)

305(80.3%) suffer from insomnia and 75(19.7%) are not. The common cause of insomnia was academic anxiety 192(64.6). And it persist for long time in 101(31.4) of them. 305 (80.3) had insomnia, and it continuous in 101 of them, the cause of insomnia in 192 of them is academic irritation 286(77.1%) have a knowledge about antihistamine 63(17.1%) use antihistamine for insomnia, 59 of them use it without prescription, the majority of them 64 did not take the same dose and 42 take the same dose,

Table 7 Correlation between dependence and abuse.

		Without prescription	Do you think you are depending on it
Spearman's rho	Without prescription	Correlation Coefficient	1.000
		Sig. (2-tailed)	-
		N	159
Do you think you are depending on it		Correlation Coefficient	0.169
		Sig. (2-tailed)	0.055
		N	130

No significant correlation

Table 8 Correlation between irrationality and abuse.

		Without prescription	Do you know what is antihistamine
Spearman's rho	Without prescription	Correlation Coefficient	1.000
		Sig. (2-tailed)	-
		N	159
Do you know what is antihistamine		Correlation Coefficient	.328**
		Sig. (2-tailed)	0.000
		N	159

** . Correlation is significant at the 0.01 level (2-tailed)

Table 9 Correlation between sex and irrational use.

		Sex	Do you use antihistamine in insomnia
Spearman's rho	Sex	Correlation Coefficient	1.000
		Sig. (2-tailed)	-
		N	384
Do you use antihistamine in insomnia		Correlation Coefficient	-.070
		Sig. (2-tailed)	.189
		N	354

No significant correlation

5 students take antihistamine at any time they feel insomnia, 8 students can't sleep without antihistamine (Figures 2 and 3).

Abuse and dependence: 89(56%) of the students use antihistamine without prescription and 5(3.8) of them are depending on it (Figure 4).

Correlations: Abuse is not correlated with age, gender, dependence and irrational use were as it correlate with level and knowledge of the students. Also no correlation between irrational use and gender but it correlate with age, level of the students and dependence (Figure 5).

Table 10 Correlation between age and irrational use.

		Age 1	Do you use antihistamine in insomnia
Spearman's rho	Age 1	Correlation Coefficient	1.000
		Sig. (2-tailed)	-
		N	380
	Do you use antihistamine in insomnia	Correlation Coefficient	-.148**
		Sig. (2-tailed)	.005
		N	351

** . Correlation is significant at the 0.01 level (2-tailed)

Table 11 Correlation between level and irrational use.

		Level	Do you use antihistamine in insomnia
Spearman's rho	Level	Correlation Coefficient	1.000
		Sig. (2-tailed)	-
		N	386
	Do you use antihistamine in insomnia	Correlation Coefficient	-.171**
		Sig. (2-tailed)	.001
		N	356

** . Correlation is significant at the 0.01 level (2-tailed)

Table 12 Correlation between dependence and irrational use.

		Do you use antihistamine in insomnia	Do you think you are depending on it
Spearman's rho	Do you use antihistamine in insomnia	Correlation Coefficient	1.000
		Sig. (2-tailed)	-
		N	356
	Do you use antihistamine in insomnia	Correlation Coefficient	.212*
		Sig. (2-tailed)	.015
		N	133

** . Correlation is significant at the 0.01 level (2-tailed)

Recommendation

The prevalence of dependence is not high but I think that is not enough to say that dependence dose not develop, also up to my knowledge this is the only study of irrationality, abuse and dependence of antihistamine in Sudan, and I think more studies are required to be done accordingly. Prescription control is required to prevent drug abuse, self- confidential and awareness courses for college student are essential to be one of the academic requirement in college stage. The concerned authority should only allow pharmacy graduates to sale the drugs, so that

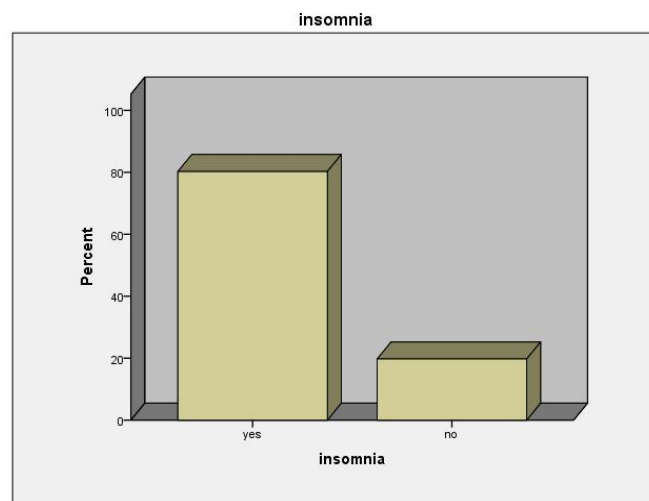


Figure 2 Prevalence of insomnia among the students.

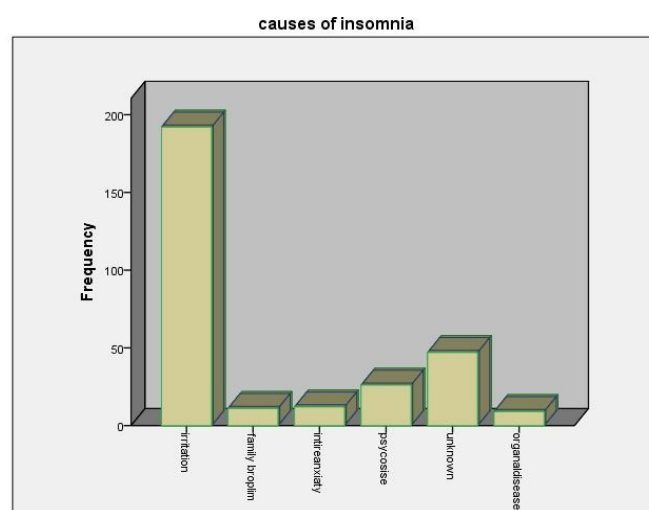


Figure 3 The causes of insomnia, the figure show that the common cause of insomnia among the student was academic irritation.

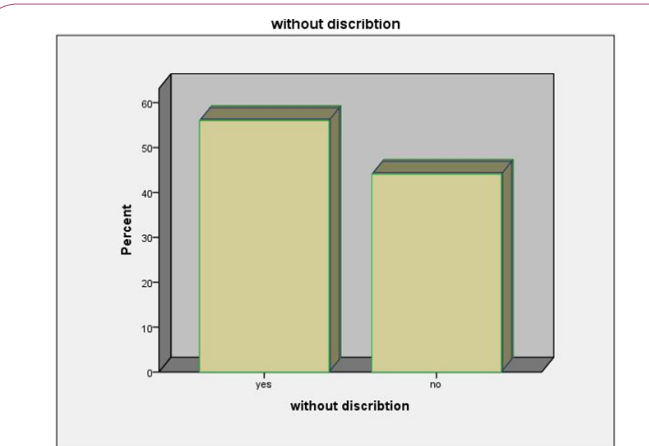


Figure 4 Prevalence of abuse.

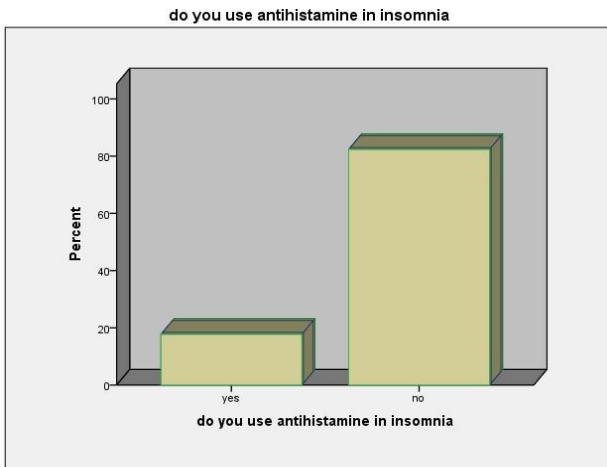


Figure 5 Prevalence of irrational use.

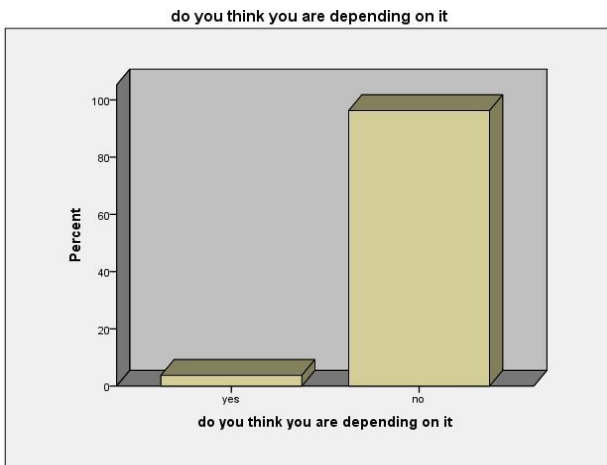


Figure 6 Prevalence of dependence among the students.

potential high risk due to drug dose, duration can be controlled to some extent (**Figure 6**).

Conclusion

The prevalence of irrational use and abuse of antihistamine is high among medical students, dependence may develop, abuse is correlated with level and knowledge, irrationality is correlated with abuse and dependence. Insomnia prevalence is very high among the students and the common cause for it is the academic irritation.

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