

Symptoms of anxiety and medication abuse in patients with chronic migraine from Trujillo, Peru

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Objective: To determine the relationship of medication abuse and anxiety symptoms in adult outpatients with chronic migraine in the SANNA / Sánchez Ferrer Clinic, Trujillo-Peru.

Material And Method: Cross-sectional study, with a sample of 104 patients with chronic migraine with and without medication abuse. Absolute, relative, average and SD frequencies are reported according to the type of variable. In the bivariate, the analysis is done through the Chi2 of Homogeneity and level of the multivariate analysis, using regression of Generalized Linear Models, Poisson and Poisson family with robust variance. **Results:** We found 96 (92.3%) female patients, with a mean age and SD 37.1 ± 9.6 . Overall, 1 in 3 patients had anxiety symptoms, and 1 in 2 patients reported medication abuse. The proportion of patients with anxiety symptoms was three times higher in the group with medication abuse than in that without medication abuse. Outpatients with chronic migraine who abuse medications are 2.28 times more at risk of anxiety symptoms than those who do not abuse medications.

Conclusions: Outpatients with chronic migraine who abuse medications have a higher risk of anxiety symptoms. Therefore, it is necessary to incorporate psychological support to all patients with medication abuse and prevent side effects of that abuse.

Key Words: Anxiety, medication abuse, Cluster Headache, Substance-Related Disorders. (Source: MeSH)

INTRODUCTION

The World Health Organization (WHO) states that at least 30% of adults between the ages of 18 and 65 worldwide suffered a migraine attack at least once in 2016⁽¹⁾. It was also the sixth most important cause of Years Lived with Disability (YLD) worldwide that year, while in Latin America, it was the seventh cause^(2,3). YLDs resulting from migraine headaches affect social activities and work differently according to gender; in women, it is three times more

frequent than in men, occurring more frequently in adults who are of production age or in work stages⁽⁴⁾.

Migraine, classified with aura and without aura, is one of the main primary headaches of the International Classification of Headaches third edition (ICHD-3) of the International Headache Society⁽⁵⁾. Migraine is episodic if its duration is less than 15 days a month; if the occurrence is more than 15 days in a month and extends for more than three months, it is considered chronic migraine. When either of

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the two types of migraine has as main cause the overuse of medications, it is classified as a secondary headache, causing YLD according to the ICHD⁽⁵⁾

Agonist drugs, also known by the name of triptans, are used to treat chronic migraine. In our country, 2 out of 7 existing worldwide are available; these are combined with steroidal anti-inflammatory drugs (NSAIDs) such as sumatriptan/naproxen, with proven efficacy to treat chronic migraine⁽⁶⁾. But, the most used are ergot alkaloids, non-selective (5-HT) agonists, with NSAIDs, which in turn can be used alone or combined with caffeine⁽⁷⁾.

The overuse of medications, such as an uncontrolled amount of ergotamines or a combination with NSAIDs with caffeine, can give rise to headaches due to drug abuse. According to ICHD, drug abuse occurs when ergotamine, triptan, opioid, or combined drugs are consumed for a period greater than ten days in a month; also, when consuming a simple analgesic for more than fifteen days in a month⁽⁵⁾. When the overuse of medications extends for up to a year, it is considered a causal risk factor in patients with episodic migraine to switch to chronic migraine⁽⁸⁾. In Peru, a study reported that 45% of adults in Cajamarca self-medicated⁽⁹⁾.

Previous studies show some risk factors for suffering from drug abuse such as old age, being a woman, higher levels of education, smoking, physical inactivity, coffee consumption,⁽¹⁰⁾ a family history of migraines⁽¹¹⁾, study and work at the same time⁽¹²⁾, and being single⁽¹³⁾.

On the other hand, worldwide, anxiety belongs to the 30% of non-fatal diseases in the world. It is estimated that, in emergencies, 1 in 5 have anxiety or depression. But little was done for prevention and clinical management, although it is estimated that the treatment of anxiety has a benefit of 400%, that is, for every 1 dollar invested, it yields 4 dollars in the clinical improvement of the patient⁽¹⁴⁾.

Anxiety disorder is defined as an anticipation of harm or misfortune that will happen in the future accompanied by feelings of dysphoria and tension; those become intense, overcoming the adaptive capacity of people, causing discomfort at a psychological, physical, and behavioral level⁽¹⁵⁾. It is characterized by the

presence of excessive worry for at least six months most of the days of each month. It does not allow the sufferer to lead a normal life, as it is difficult to control that worry. In addition to excessive worry and lack of control, other symptoms are restlessness or a feeling of being trapped, muscle tension, sleep disorders, difficulty concentrating, irritability, and fatigue⁽¹⁶⁾. The National Institute of Mental Health (NIMH) affirms that genetic and environmental factors, plus the interaction with other factors such as shyness, being a woman, having few economic resources, and exposure to stressful events could generate a greater probability of suffering from anxiety disorder⁽¹⁷⁾.

Some risk factors for anxiety have already been identified and reported in the scientific literature. Among them are depression⁽¹⁸⁾, diabetes⁽¹⁹⁾, hypertension⁽²⁰⁾, hearing impairment⁽²¹⁾, smoking⁽²²⁾, alcohol consumption⁽²³⁾, breast cancer⁽²⁴⁾, peripheral arterial disease⁽²⁵⁾, domestic violence⁽²⁶⁾, child abuse⁽²⁶⁾, limitation of sports activity⁽²⁷⁾, prescription drug abuse⁽²⁸⁾, being female⁽²⁹⁾, older age⁽³⁰⁾, higher education levels⁽³¹⁾, being widowed or divorced⁽³²⁾, and having some work occupation⁽³³⁾.

Within the Peruvian context, on these variables, studies show the prevalence of migraines in general populations⁽³⁴⁾⁽³⁵⁾, pregnant women⁽³⁶⁾⁽³⁷⁾, and university populations⁽³⁸⁾⁽³⁹⁾. However, there is little knowledge of the association of drug abuse with anxiety symptoms in patients with chronic migraine. Understanding this association can provide useful information for suggesting ways or forms to reduce the world loads of psychological illnesses such as anxiety symptoms that are modifiable

Faced with this, the objective of the present study was to determine the relationship of anxiety symptoms and drug abuse in adult outpatients with chronic migraine at the SANNA / Sánchez Ferrer Clinic, Trujillo-Peru.

METHODOLOGY

Design of the research

Cross-sectional study, developed from the data requested from the SANNA/Sánchez Ferrer Clinic in the city of Trujillo/La Libertad, Peru, in 2019.

Participants

Study participants were patients who were seen between January 2018 to April 2019 at the SANNA / Sánchez Ferrer Clinic in the city of Trujillo / La Libertad, Peru.

The data were extracted with prior authorization from the clinic, only for the purposes of this study and without identifying information of any participant. These patients were registered in ambulatory care. For this study, data were requested from patients with ages greater than or equal to 18 years of chronological age and who had a diagnosis of suffering from chronic migraines. Likewise, patients who reported suffering from diseases other than chronic migraine, such as headaches, with acute febrile illness, metabolic diabetic kidney or liver disease, cancer, human immunodeficiency virus (HIV), and arterial hypertension, were excluded.

Sample

The sampling was conducted from the dependent variable,

$$\frac{Z_{\alpha/2}^2 \cdot x p \cdot x q}{e^2}$$

anxiety symptoms, in patients with chronic migraine. While the sample size was calculated by random sampling simple in unknown population, using the following formula; therefore, the calculated sample size was (n = 96). However, to give greater power to the sample and due to the availability of data, one (n = 104) participant was taken.

Procedures

Initially, a document was sent requesting the data of patients with chronic migraine from January 2018 to April 2019. It was explained that the data would be used to conduct research work. Once the database was obtained, it was registered in a folder with a password and for the exclusive use of the main researcher.

For data cleansing, only patient data that had all fields complete were considered, and incomplete data were removed. To consider that a patient had complete data, they had to show at least a diagnosis of chronic migraine and age, gender, marital status, occupation, level of education, drug abuse, and anxiety symptoms

because they performed the construction of the directed acyclic graph (GAD) and in the database, only the following variables could be obtained (Complementary material).

Instruments and variables

The anxiety symptoms variable was determined through the Patient Health Questionnaire (PHQ-4)⁽⁴⁰⁾, from which Cronbach's Alpha ($\alpha = 0.07$) was estimated. It showed acceptable levels of reliability in the Peruvian population with chronic migraine. To determine the presence of anxiety symptoms, the direct score of items 3 and 4 should be ≥ 3 .

The drug abuse variable was determined by a neurologist of the staff of the SANNA/ Sánchez Ferrer Clinic in the city of Trujillo, classifying patients as with/without drug abuse. For this diagnosis, the diagnostic manual of the International Headache Classification third edition (ICHD-3) of the International Headache Society was used⁽⁵⁾.

Thus, sociodemographic data such as age, gender, marital status, occupation, degree of education were also considered because the scientific literature indicated that they were related to at least one of the outcome and exposure variables (Complementary material).

Statistical Analysis

For the univariate analysis, absolute and relative frequencies were reported for the categorical variables, and the mean and standard deviation were estimated for the quantitative variables. In the bivariate analysis, the Chi-square test of homogeneity was used to evaluate the association between sociodemographic variables, drug abuse, and anxiety symptoms. While in the multivariate analysis, the regression of Generalized Linear Models, family Poisson, and link function log, considering the robust variance estimator [vce(robust)] due to non-convergence; to determine the association between drug abuse and anxiety symptoms, in crude analysis and adjusted for confounders.

The assumptions of the regression used, independence of events, constant over time, and equidispersion, were met. Given the number of confounding variables, the variance inflation factor was used (VIF) to evaluate the presence of collinearity; variables with VIF <10 entered

the adjusted model. The statistical analysis was performed in STATA 14 for Windows (STATA Corp, College Station, TX, USA).

Ethical Aspects

The present study respected the principles of research in humans of the Declaration of Helsinki⁽⁴¹⁾. Likewise, it was approved by the Ethics Committee of the Antenor Orrego Private University of the city of Trujillo, Peru.

RESULTS

It was found that (92.3%) were female, the average age and SD was 37.1 ± 9.6 , the majority 90 (86.5%) had secondary education or more, 55 (52.9%), reported being employed, and 61 (58.7%) were married. Likewise, the majority,

meaning 58 (55.8%) reported drug abuse and 37 (35.6%) had anxiety symptoms (Table 1). In the bivariate analysis, 36 (37.5%) female patients, 1 (12.5%) male patient, patients with an average age of 36 years old, 5 (35.7%) patients with primary education or none, and 32 (35.6%) patients with secondary education or more, had anxiety symptoms. In regards to occupation, 14 (41.2%) patients were homemakers, 18 (32.7%) patients were employed, 5 (33.3%) patients were self-employed. In regards to marital state, 12 (41.4%) patients were single, 21 (34.4%) patients were married, and 4 (28.6%) patients were widowed. Lastly, 9 (19.6%) patients did not abuse drugs 28 (48.3%) patients did abuse drugs. Likewise, a significant relationship between drug abuse and anxiety symptoms was determined ($p=0.002$) (Table 2).

Table 1. Characteristics of adult outpatients with chronic migraine, Trujillo-Peru.

Features	n (%)
Sex	
Male	8 (7.7)
Female	96 (92.3)
Age	37.1 ± 9.6
Years of schooling	
Primary or none	14 (13.5)
Secondary education or more	90 (86.5)
Occupation	
Homemaker	34 (32.7)
Employed	55 (52.9)
Self-employed	15 (14.4)
Marital state	
Single	29 (27.9)
Married	61 (58.7)
Widower	14 (13.5)
Drug abuse	
No	46 (44.2)
Yes	58 (55.8)
Anxiety Symptoms	
No symptoms	67 (64.4)
With symptoms	37 (35.6)

In the raw multivariate analysis, an association was found between drug abuse and anxiety symptoms with (RP= 2.47; IC 95%: 1.29 - 4.71; p= 0.006). This association was maintained in the adjusted analysis (RP= 2.28; IC 95%: 1.17 - 4.47; p= 0.016) (Table 3).

DISCUSSION

It was found that those who abuse drugs have a 2.28 higher risk to suffer from anxiety symptoms than those who do not abuse drugs (RP= 2.28; IC 95%: 1.17 - 4.47; p= 0.016). In this regard, it was not possible to evidence the existence of previous studies in the primary population or from secondary databases, until May 2019. However, a review study provides an approximation of the relationship between

excessive use of medications and anxiety in adult patients with headaches, which may also generate fear of headaches and psychological dependence on drugs⁽²⁸⁾. The relationship between overuse of medications and symptoms of anxiety may be behavioral in nature, since overuse of medications is the main cause of chronic migraine. This is characterized by generating intense headaches for at least 15 days a month (daily) in periods greater than 3 months⁽⁵⁾.

Due to the effect of the medication, which is the reduction of chronic migraine headaches, by ceasing to feel that effect on the pain due to the lack of consumption of the medication, the patient generates fear of pain, causing concern, which becomes difficult to control. Likewise, abstinence from medication due to the neglect of

Table 2. Relationship between drug abuse and anxiety symptoms in adult outpatients with chronic migraine from Trujillo-Peru.

Variables	Anxiety symptoms		p*
	Without symptoms (n=67)	With symptoms (n=37)	
Sex			0.156
Male	7 (87.5)	1 (12.5)	
Female	60 (62.5)	36 (37.5)	
Age	37.8 ± 9.6	35.7 ± 9.6	
Years of schooling			0.688
Primary education or none	9 (64.3)	5 (35.7)	
Secondary education or none	58 (64.4)	32 (35.6)	
Occupation			0.707
Homemaker	20 (58.8)	14 (41.2)	
Employed	37 (67.3)	18 (32.7)	
Self-employed	10 (66.7)	5 (33.3)	
Marital state			0.684
Single	17 (58.6)	12 (41.4)	
Married	40 (65.6)	21 (34.4)	
Widower	10 (71.4)	4 (28.6)	
Drug abuse			0.002
No	37 (80.4)	9 (19.6)	
Yes	30 (51.7)	28 (48.3)	

* Chi2 homogeneity with Fisher's exact test

Table 3. Poisson regression analysis of the relationship between drug abuse and anxiety symptoms in adult outpatients with chronic migraine from Trujillo-Peru.

Variables	Raw analysis		Adjusted analysis*	
	RP (CI 95%)	p	RP (CI 95%)	p
Age**	0.99 (0.96 - 1.01)	0.300		
Sex				
Male	Ref.		Ref.	
Female	3.00 (0.47 - 19.28)	0.247	2.26 (0.46 - 11.05)	0.315
Years of Schooling				
Less than secondary education	Ref.		Ref.	
Higher than secondary education	1.00 (0.47 - 2.13)	0.991	1.12 (0.54 - 2.32)	0.759
Occupation				
Homemaker	Ref.		Ref.	
Employed	0.79 (0.46 - 1.38)	0.417	0.88 (0.51 - 1.55)	0.667
Self-employed	0.81 (0.35 - 1.85)	0.616	0.85 (0.39 - 1.85)	0.683
Marital state				
Single	Ref.		Ref.	
Married	0.83 (0.48 - 1.45)	0.518	0.75 (0.43 - 1.30)	0.307
Widower	0.69 (0.27 - 1.77)	0.440	0.75 (0.31 - 1.80)	0.521
Drug Abuse				
No	Ref.		Ref.	
Yes	2.47 (1.29 - 4.71)	0.006	2.28 (1.17 - 4.47)	0.016

Abbreviations: RP, Risk of prevalence; CI, confidence interval.

* Adjusted for: sociodemographic variables and family history

** age presented VIF > 10 and withdrew for adjusted analysis.

the dose and/or schedules for the consumption of the medication, or the attempt to abandon the overuse of medications, cause nervousness in the patient, that leads to psychological dependence on medications.⁽²⁸⁾ In this way, the abuse of medications could generate the risk for generalized anxiety, since difficult-to-control worries and anxious nervousness are some of its main symptoms.⁽¹⁶⁾

It is worth mentioning that this relationship was previously shown in a case study, where a patient with asthma and drug abuse suffered generalized anxiety due to drug withdrawal⁽⁴²⁾. This shows the external consistency of the results of the present study: since it is possible that the risk relationship between drug abuse and anxiety

symptoms is not only present in populations with chronic migraine, consequently, it could represent a health problem public--neglected until now.

Overall, 1 in 3 patients had symptoms of anxiety, and 1 in 2 patients reported drug abuse. While, when analyzed by subgroups, the proportion of patients with anxiety symptoms was three times higher in the group of those who abuse drugs compared to those who do not abuse drugs, this difference was significant ($p = 0.002$). In this regard, the scientific literature affirms the coexistence of drug abuse with anxiety symptoms⁽²⁸⁾. This could be because of drug abuse occurring due to dependence on it, which has symptoms of anxiety and nervousness due

to the absence of the effect of the drug medicine for chronic migraine pain⁽²⁸⁾, thus causing such coexistence.

It is important to disclose some limitations in this study: First, the instrument used in this study has not been validated in the Peruvian population, rather it was taken from the validation in the Colombian population⁽⁴³⁾; however, it is an instrument, easy to understand, also, when analyzing the Cronbach's Alpha ($\alpha = 0.07$) showed acceptable levels of reliability of the PHQ-4 in the Peruvian population of outpatients with chronic migraine.

Second, because they are secondary data and data are used as they are found when consulting the medical staff of the SANNA Clinic about the collection of "marital status", they indicated patients self-reported the data. Therefore, it is very likely that in the group of "married" they are both cohabiting and married patients. Likewise, in terms of occupation, it is likely that those who report being a housewife, employed, and independent also perform as undergraduate or graduate university students or have more than one work activity. The general way in which the information was collected could have influenced the non-significance of the relationship with anxiety symptoms. But that does not detract from our findings, as it is a first approximation of the relationship between drug abuse and anxiety symptoms.

Likewise, it is suggested that subsequent studies on the relationship between drug abuse and anxiety symptoms should be in the primary population and also use means of verification of self-reported data such as sociodemographic data.

The strength of the present study lies in that it is the first approximation at a national level on drug abuse and its relationship with anxiety symptoms, with external validity of its results on the relationship of these variables in other diseases⁽⁴²⁾. This has not been explored until now. Additionally, the results show a gap in Peruvian public health, because to date, at the Latin American level, there is no clinical practice guide for anxiety care in patients with drug abuse, nor an action plan or promotional, preventive activities. Because anxiety symptoms are modifiable factors that, if they were modified, they could improve the health of

the patient⁽⁴⁴⁾ and bring a better quality of life to the patient who suffers from chronic migraines.

CONCLUSIONS

Ambulatory patients with chronic migraines who abuse drugs have a 2.28 increased risk to suffer anxiety symptoms than those who do not abuse drugs.

Overall, 1 in 3 patients had symptoms of anxiety, and 1 in 2 patients reported drug abuse. The proportion of patients with anxiety symptoms was three times higher in the drug abuse group than in the non-drug abusers.

Our results may be the basis to be able to explore in greater depth the relationship between these variables. Likewise, decision-makers could support, with our results, the implementation of policies to prevent and treat anxiety in patients with chronic migraines who suffer from drug abuse.

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