ORIGINAL ARTICLE

# Factors associated with acute medication overuse in chronic migraine patients

## Fatores associados ao uso excessivo de medicação sintomática em pacientes com enxaqueca crônica

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## ABSTRACT

**Objective:** To evaluate the prevalence of psychiatric disorders in patients diagnosed with chronic migraine with and without acute medication overuse. **Methods:** Seventy-two volunteers were recruited from a Family Health Program of the Paraisópolis community in São Paulo (SP), Brazil. These patients were submitted to a detailed headache questionnaire. All participants were submitted to physical and neurological examinations. The following variables were analyzed: age, gender, education level, body mass index, type of overused medication, headache characteristics, and caffeine consumption, lifetime anxiety and mood disorders. **Results:** Out of 72 patients, 50 (69%) had chronic migraine with medication overuse, and 22 (31%) had chronic migraine without medication overuse. Factors such as age, gender, education level, body mass index, type of overused medication, headache characteristics, and caffeine consumption were not significantly different between the two studied groups. Lifetime anxiety and mood disorders were more common in patients with acute medication overuse ($p=0.003$ and $p=0.045$, respectively). **Conclusion:** This study has shown a significant association among chronic migraine and medication overuse with lifetime mood and anxiety disorders in patients of the studied population. No association was found for other researched psychiatric disorders.

**Keywords:** Migraine disorders/drug therapy; Chronic disease; Mental disorders; Prevalence; Comorbidity

## RESUMO

**Objetivo:** Avaliar a prevalência de transtornos psiquiátricos em pacientes com diagnóstico de enxaqueca crônica com e sem uso excessivo de medicação sintomática. **Métodos:** Setenta e dois voluntários foram recrutados a partir de um Programa de Saúde da Família da comunidade de Paraisópolis, na cidade de São Paulo (SP). Esses pacientes foram submetidos a exames clínico e neurológico. As seguintes variáveis foram analisadas: idade, gênero, nível educacional, índice de massa corporal, tipo de uso excessivo de medicação, características da cefaleia, consumo de cafeína, presença de ansiedade e distúrbios de humor. **Resultados:** Dos 72 pacientes, 50 (69%) tinham cefaleia crônica, com uso exagerado de medicação, e 22 (31%) tinham cefaleia crônica, sem uso excessivo de medicação. Os fatores idade, gênero, nível educacional, índice de massa corporal, tipo de uso excessivo de medicação, características da cefaleia e consumo de cafeína não mostraram diferença significante entre os grupos estudados. Os diagnósticos de ansiedade e de distúrbios de humor ao longo da vida foram mais comuns nos pacientes com uso excessivo de medicação ($p=0,003$ e $p=0,045$, respectivamente). **Conclusão:** Este estudo mostrou uma associação significativa entre cefaleia crônica e uso excessivo de medicação nos pacientes avaliados, quanto ao diagnóstico de transtornos de ansiedade e de humor ao longo da vida. Não foi encontrada nenhuma associação com outros distúrbios psiquiátricos pesquisados.

**Descritores:** Transtornos de enxaqueca/quimioterapia; Doença crônica; Transtornos mentais; Prevalência; Comorbidades

## INTRODUCTION

Migraine is considered a chronic, disabling disease which significantly reduces quality of life, and has a considerable economical impact[1,2]. Medication overuse headache (MOH) according to the diagnostic

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criteria of the International Headache Society (IHS) review and its attachment (IHS-2004/2006)[3,4] for chronic migraine (CM) with and without medication overuse is an important factor in the transformation of episodic migraine into CM[5]. In the case of ergotamine, triptans, opioids and combination medications in particular, intake on >10 days/month for >3 months is required, whereas simple analgesics are considered overused when they are taken on >15 days/month for >3 months.

Epidemiological studies suggest that up to 4% of the population may overuse analgesics and other symptomatic medications for management of pain disorders like migraine[6]. MOH occurs in about 1% of the adult population and in 0.5% of adolescents[6] from Europe, North America, and Asia[7,8].

MOH can be distinguished as simple (Type I) or complex (Type II). Simple cases involve relatively short-term drug overuse, relatively modest amounts of overused medications, minimal psychiatric contribution, and no history of relapse after drug withdrawal. In contrast, complex cases may involve long-term use of daily opioids or combined analgesics, multiple psychiatric comorbidities, and/or a history of relapse. Daily use of opioids for other medical conditions, and psychiatric comorbidity including borderline personality disorder, prior history of other substance dependence or abuse, and family history of substance related disorders are risk factors for MOH. Although limited, current research suggests that comorbidity psychiatric disorders are more prevalent in MOH than in control headache conditions, and may precede the onset of MOH. Such cases appear to have an elevated risk of family history of the use of substance related disorders in MOH patients, and an increased risk of MOH in patients diagnosed with personality disorders[9,10].

Mathew[11] was one of the first to point out the connection between transformed migraine and anxiety, depression and insomnia, having identified mood and anxiety disorders in 70% to 80% of patient. According to another research 58,7% of the CM patient had moderate or severe depression[12].

Even though psychiatric comorbidity in CM and the influence of acute medication overuse in this disease are well known, little has been enlightened on the connection between these two aspects[13]. In case of patients that are refractory to the treatment, such connection requires further research.

## OBJECTIVE

To investigate psychiatric disorders among CM patients with and without influence of acute medication overuse.

## METHODS

We analyzed data from 86 volunteers recruited from a Family Health Program (PSF) of the Paraisopólis community, in the city of São Paulo (SP), Brazil.

At the first moment, patients were submitted to a detailed headache questionnaire, and to physical and neurological examinations. In doubtful cases of secondary headaches, appropriate investigation was performed by the same trained clinician and confirmed by the neurology team. Out of this total, 14 patients were excluded: 6 had secondary headache due to idiopathic intracranial hypertension, 1 had hypophyseal macroadenoma, 1 had right ophthalmic artery aneurysm; 1 had secondary headache attributed to rhinosinusitis, or to moderate or severe head injury, and 5 due to alcohol abuse.

The patients assessed were in the 18 to 65 age group (36.4±9.5 *versus* 40.2±11.3 years old), being 61 women and 11 men divided into two groups. Group 1 CM had headache present on ≥15 days per month, without the influence of acute medication overuse, whereas Group 2 CM had headache for ≥15 days per month with the influence of acute medication overuse.

The diagnosis for headache was established according to the diagnostic criteria of the IHS review and its attachment (IHS-2004/2006)[3,4] for CM with and without medication overuse. By then, the patients had had headaches with those features for at least 6 months.

The categories of overused symptomatic medications varied from simple analgesics to narcotics, triptans and combinations of ergot derivatives and caffeine, analgesics and caffeine (Table 1).

All patients were interviewed by a psychologist and a psychic profile was assessed by the SCID 1/P[14], a structured interview for psychiatric disorders based on the DSM-IV diagnostic criteria[15] and International Statistical Classification of Diseases and Related Health Problems (10th Revision Version for 2007).

The Migraine Disability Assessment (MIDAS) score[16] was used. Anxiety symptoms severity was assessed according to the Hamilton Anxiety Scale (HAM-A) [17] and the Spielberg-State-Trait Anxiety Inventory[18]. Depression symptoms were assessed according to the Beck's Depression Inventory (BDI-II)[19] and the Hamilton Depression Scale (HAM-D)[20].

The research protocol was reviewed and approved by the local Research Ethics Committee. All patients signed the informed consent form.

The $X^2$ test (without the Yates correction), or the Fisher's Exact Test (in case the contingency table

presented an expected value <5), was used for data comparison. Differences among continuous data averages were tested by parametric and non-parametric tests, which showed, without exception, similar results. Only the parametric test results will be displayed. The Student's *t* test was used for independent samples and the Mann-Whitney's test for their non-parametric equivalent.

Statistical significance was considered when $p<0.05$. All tests were two tailed. Ninety-five percent of Confidence Interval (CI) was calculated in relation to the differences among averages. The whole analysis was calculated according to the Statistical Package for the Social Science (SPSS) 11.5.1 for Windows.

## RESULTS

Seventy-two patients with CM were included. Twenty-two (31%) had CM without MOH and 50 (69%) had CM with MOH.

The socio-demographic data and clinical characteristic, such as age [36.4±9.5 *versus* 40.2±11.3 years; 95%CI=-9.2-1.8; $t(70)=-1.3$; p=0.183]; gender (31% male *versus* 69% female; Fisher's exact test; p=1.000); education level (1.3±0.7 *versus* 1.4±0.7 years; 95%CI=-0.4-0.3; $t(59)=-0.3$; p=0.734); body mass index [24.7±4.3 *versus* 25.5±4.7kg/m$^2$; 95%CI=-3.0-1.6; $t(70)=-0.6$; p=0.537] were not significant enough to differentiate the patients with MOH from those without MOH.

Patients with and without MOH had similar characteristics of pain: time of daily pain in years [17.3±10.6 *versus* 19.6±12.4; 95%CI=-8.4-3.7; $t(70)=-0.8$; p=0.443]; the duration of the crisis in hours [20.6±14.2 *versus* 17.7±10.7; 95%CI=-3.5-9.2; $t(66)=0.9$; p=0.373] did not differ for pain relief.

The type of overuse medication used for pain relief was not significant enough to differentiate the patients with MOH from those without MOH (Table 1).

In this study, 50% of patients with CM and MOH fulfilled the criteria for current major depressive episode (MDE); 59% for past MDE, specific phobia and lifetime mood disorder; 39% for major depressive disorder (MDD); 27% for social phobia, 9% for panic and obsessive-compulsive disorder; 68% for generalized anxiety disorder; and 23% for post-traumatic stress disorder. Of the three significantly more frequent diagnoses in this study, two belonged to the group of anxiety disorders (generalized anxiety disorder=68%, specific phobia=59%); the third, major depression (59%) is often followed by important anxious symptoms, fear and avoidance behavior.

In MOH patients, the diagnosed lifetime anxiety and mood disorders were statistically significant (p=0.003 and p=0.045, respectively) (Table 2).

In none of the psychiatric scales used were the scores significantly different, in statistical terms, between the two groups of patients (Table 3).

**Table 1**. Comparison of the frequency distribution of medications in patients with and without medication overuse headache

| Drugs | With MOH (%) | Without MOH (%) | $\chi^2$ | p-value |
|---|---|---|---|---|
| Dipyrone | 82 | 88 | _ | 0.482 |
| Orphenadrine | 9 | 14 | _ | 0.712 |
| Isometepten | 23 | 34 | 0.91 | 0.339 |
| Promethazine/adiphenine | 14 | 14 | _ | 1.000 |
| Acetylsalicylic acid | 27 | 28 | 0.00 | 0.949 |
| Paracetamol | 27 | 24 | 0.09 | 0.768 |
| Caffeine | 50 | 58 | 0.40 | 0.529 |
| NSAIDs | 4 | 12 | _ | 0.427 |
| Others | 4 | 8 | _ | 1.000 |

$\chi^2$ test or Fisher's exact test.
MOH: medication overuse headache; NSAID:non-steroidal anti-inflammatory drug.

**Table 2.** Comparison of the frequency distribution of the qualitative psychiatric diagnosis of patients with and without medication overuse headache

| Characteristics | Without MOH (%) n=22 (31%) | With MOH (%) n=50 (69%) | $\chi^2$ | p-value |
|---|---|---|---|---|
| Current MDE | 53 | 50 | 0.04 | 0.848 |
| Past MDE | 42 | 59 | 1.54 | 0.214 |
| MDE | 37 | 39 | 0.02 | 0.893 |
| Specific phobia | 42 | 59 | 1.54 | 0.214 |
| Social phobia | 16 | 27 | _ | 0.520 |
| Panic | 21 | 9 | _ | 0.229 |
| Generalized anxiety disorder | 63 | 68 | 0.15 | 0.698 |
| PTSD | 16 | 23 | _ | 0.738 |
| OCD | 5 | 9 | _ | 1.000 |
| Current anxiety disorder | 63 | 82 | _ | 0.196 |
| Lifetime anxiety disorder | 47 | 84 | 9.08 | 0.003* |
| Current mood disorder | 37 | 52 | 1.27 | 0.287 |
| Lifetime mood disorder | 32 | 59 | 4.01 | 0.045* |
| Others | 16 | 18 | _ | 1.000 |

* p value <0.05.
$\chi^2$ test
MOH: medication overuse headache; MDE: major depression episode; PTSD: post-traumatic stress disorder; OCD: obsessive-compulsive disorder.

**Table 3**. Comparison between the scores in the psychiatric scales got by patients with and without medication overuse headache

| Questionnaires | MOH mean (±SD) | | 95%CI (diference) | *t* | DF | p-value |
|---|---|---|---|---|---|---|
| | Without | With | | | | |
| MIDAS | 22.1 (30.6) | 29.3 | 11.4 | -0.8 | 60 | 0.440 |
| HAM-A | 14.1 (8.1) | 14.3 | 4.3 | -0.1 | 60 | 0.931 |
| HAM-D | 12.4 (8.6) | 11.9 (6.7) | -3.6-4.4 | 0.2 | 61 | 0.828 |
| BDI | 12.8 (8.1) | 15.2 (10.1) | -7.7-2.8 | -0.9 | 60 | 0.362 |
| Spielberg state | 40.8 (8.5) | 45.4 (13.1) | -11.2-1.9 | -1.4 | 61 | 0.162 |
| Spielberg trait | 46.6 (10.7) | 49.1 (12.8) | -9.2-4.2 | -0.7 | 61 | 0.458 |
| PCS | 214.7 (66.0) | 198.1 (76.3) | -27.4-60.7 | 0.8 | 47 | 0.451 |
| MCS | 215.2 (93.2) | 218.8 (82.4) | -55.7-48.5 | -0.1 | 47 | 0.891 |

MOH: medication overuse headache; SD: standard deviation; CI95%: 95% confidence interval; *t*: Student's t test for independent samples; MIDAS: migraine disability assessment; HAM-A: Hamilton anxiety scale; HAM-D: Hamilton depression scale; BDI: Beck depression inventory; PCS; physical component summary; MCS: emotional component summary.

## DISCUSSION

The findings of the present study did not show a statistically significant difference between the groups of patients with and without MOH related to age, gender, education level, body mass index, and quality of life. On the other hand, the literature shows a lifetime prevalence of 16% in the general population, namely, 8% among men and 25% among women[21].

The two groups of patients studied have shown similar pain characteristics, which is consistent with the literature descriptions[22].

The type of medication used to relieve the pain did not appear to be a relevant differential factor between patients who overuse analgesics and those who do not, given that the results in this study did not show relevant statistical differences between the both groups. Granella et al.[23] have shown medication overuse in percentages varying from 24 to 76.1%. Yet Castillo et al.[24] have mentioned a rate of 31.1% for CM patients with medication overuse, emphasizing that the figures of this behavioral pattern differ between populations of patients from specialized health centers and random samples.

Other authors[25-29] have shown that in about 90% of the CM patients, the types of substances overused differ. The most frequently used medications are the combinations of ordinary analgesics with caffeine and other substances.

Spierings et al.[30] have shown that 22% of their samples used 300mg of caffeine per day, but 35% consumed between 100 and 300mg of caffeine daily, and 48% below 1,000mg of salicylic derivatives or its equivalent per day. These figures are not consistent with our results, which suggest a prevalence of 84% of analgesics containing caffeine.

The issue of psychiatric comorbidities is very important to establish analgesic overuse in CM. The opposite may also occur, that is, a mental disorder diagnosis could be the primary origin of medication overuse.

A retrospective study about the order of occurrence of disorders showed that, in the MOH Group, psychiatric disorders occurred significantly more often before the transformation from migraine into MOH than afterwards. MOH patients have a greater risk of suffering from anxiety and depression, and these disorders may be a risk factor for the evolution of migraine into MOH. Moreover, MOH patients have a greater risk of suffering from substance-related disorders than migraineurs sufferers. This could be because MOH is part of the spectrum of addictive disorders[31].

Anxiety disorders are considered as the most prevalent psychiatric disorders group in adults (around 25%) from the general population[13]. Regier et al.[32] also shown that the anxiety disorders as a whole represent the most prevalent group of mental disorders among the population. A further study, the National Comorbidity Survey, confirmed a lifetime anxiety disorder prevalence of 24%[13].

The pathophysiology of anxiety is attributed to a deficiency on the dopaminergic and serotoninergic neurotransmission; however, the changes in GABA receptors have lately been considered as relevant in its genesis[33]. These mechanisms may also be part of the migraine pathophysiology.

The behavioral and psychological mechanisms involved in CM as a consequence of medication overuse are complex. The route of administration, individual's genetic component, history of some other type of addiction, stress and traumatic life events, fear of having a headache and losing a job or missing an important social event, as well as the sense of relief provided by the analgesic, have a rewarding effect upon the patient that encourages him/her to continue taking more and more analgesics and, as a consequence, rebound headache due to acute medication overuse appears[33].

The present study has shown a significant association among MOH and lifetime mood and anxiety disorders.

Corchs et al.[34] and Peres et al.[35] observed that anxiety and mood scores were higher among phobic patients and that the number of phobias had a positive correlation with the degree of anxiety and depression[36]. Avoidance and fear of having a headache may also underlie analgesic consumption in CM patients.

Patients of this study were referred for humor and anxiety assessment by means of scales. These scales, however, only identify the symptoms and not determine an appropriate psychiatric diagnosis, which may even encourage, in this population, a false-negative psychological aspect.

Psychological factors may play a major role in the natural history of MOH. This is an underexplored area of clinical research that deserves further attention. In CM patients, the diagnosis for lifetime anxiety and mood disorders may help to avoid acute medication overuse.

Our study has limitations and cannot be generalized to other patients. Even though the number of patients analyzed has statistical value, it may not be large enough to detect a subtler difference. This is a transverse analysis; no patient was followed-up to determine the disease progression and chronification. A longitudinal design would be more informative, but its complex nature also makes it difficult to perform or establish confounding variables.

## CONCLUSION

This study has shown a significant association among MOH patients with lifetime mood and anxiety disorders in the studied population. Other psychiatric disorders did not show association with MOH. These findings may help to avoid acute medication overuse.

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