Background and Purpose To determine the relationships between the ruminative thought style, parameters of psychological distress, and the occurrence of medication-overuse headache (MOH).

Methods The study included 164 subjects: 83 patients (11 males and 72 females) who were first diagnosed as MOH, and 81 healthy subjects (22 males and 59 females) as a control group (CG). The study participants were aged 40.2±11.9 years (mean±standard deviation), and they were assessed using the Ruminative Thought Style Questionnaire and Depression Anxiety Stress Scales.

Results The degree of rumination was higher in patients with MOH than in the CG (p<0.001). Among patients with MOH, females, patients with comorbidities, and those who overuse combined analgesic therapy had a higher degree of rumination (p=0.038, p=0.008, and p=0.015, respectively). In both the MOH patients and CG, the degree of rumination was directly correlated with depression, anxiety, and stress (r=0.473–0.557, p<0.001, for MOH; r=0.303–0.322, p<0.005, for CG). Rumination and anxiety were associated with MOH [odds ratio (OR)=1.123, 95% confidence interval (CI)=1.071–1.178, p<0.001; OR=1.091, 95% CI=1.005–1.185, p=0.039; respectively]. The analysis of the mediation model showed that the link between rumination and MOH is largely direct (86%), and to a lesser extent is additionally influenced by anxiety as a mediator (14%).

Conclusions A ruminative thought style is associated with MOH both directly and via anxiety. Psychological strategies aimed at decreasing ruminative responses and anxiety could be useful in the prevention of MOH in selected patients.

Key Words medication-overuse headache, ruminative thought style, anxiety.

INTRODUCTION

The negative impact of medication-overuse headache (MOH) has large negative impacts on the personal, family, and social aspects of the quality of life of affected patients. The general and healthcare-specific financial costs related to MOH have been assessed as very significant.1-3 While the pathophysiology of MOH has not been fully elucidated, it might be linked to psychological and personality traits. The onset of MOH depends on parameters related to previous headache and the frequency of using therapy to stop acute headache attacks, and also on comorbid conditions, anxiety, depression, stress, unhealthy lifestyle factors (e.g., smoking, physical inactivity, and obesity), and the genetic predisposition.4-6 Psychological and personality traits, difficulties in regulating emotions and controlling one’s own behavior, introversion, less socially oriented tendencies, as well as perfectionist and dysphoric characteristics have also been linked to MOH.7-9

Psychological problems are common among patients with chronic headache,10 and some

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of them might be associated with MOH. Rumination is defined as frequent intrusive thoughts that tend to repetitively and consciously focus on a specific subject, which can also appear in the absence of relevant environmental stimuli.\textsuperscript{10-13} It has been shown that ruminative thoughts in response to painful experiences intensify psychological distress and reduce the problem-solving capability.\textsuperscript{14} However, the association between the ruminative thought style and the occurrence of MOH has not been evaluated previously.

The aim of this study was to determine the relationship between the ruminative thought style and the occurrence of MOH, and identify the possible roles of other parameters of psychological distress (e.g., depression, anxiety, and stress) in this relationship.

**METHODS**

The observational study was approved by the Ethics Committee of the Faculty of Medicine at the University of Niš.

**Study population**

After providing voluntary written informed consent to participate in the study, all of the study subjects completed a sociodemographic and medical questionnaire that included demographics, education level, marital status, family situation, and work status, number of family members, place of residence, personal medical history, presence of other illnesses, presence of previous primary and/or secondary headaches (their type, characteristics, duration, and frequency, and the effectiveness of symptomatic and preventive therapies), and habits and risk factors (e.g., physical activity, cigarette smoking, alcohol consumption, and excessive consumption of caffeine, defined as more than three cups of coffee daily). The study was conducted in the Headache Center of the Neurology Clinic at the Clinical Center in Niš during January to December 2019. The Clinical Center in Niš is a tertiary healthcare institution that serves about 2 million inhabitants in southeastern Serbia.

**Control group**

Healthy subjects for inclusion as a control group (CG) were recruited from relatives and friends of all patients who were otherwise examined in our headache clinic during the study period, after their had voluntarily agreed to participate. These subjects were included consecutively until their number reached that predicted for the number of patients in the MOH group. The inclusion criteria for the CG were based on self-reports that they had not experienced a headache of any kind within the previous 2 years, did not have other diseases, and were not receiving any chronic therapy.

**MOH patients**

This MOH group included all consecutive patients in whom MOH was first diagnosed during the period of the study. These headache patients were referred by a primary-care physician or by a specialist in neurology, internal medicine, or related specializations. Patients with previously diagnosed MOH were not included in this study in order to avoid applied pharmacoprophylaxis or other therapies influencing the examined parameters.

MOH was diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders.\textsuperscript{4} Secondary etiologies of the headaches were excluded after complete diagnostic processing. Computed tomography or magnetic resonance imaging was performed in all study patients, with normal findings for all of them. All of the headache diagnoses was made by the same physician, who is a specialist in neurology and pain medicine and is a chief at the Headache Center.

The following data regarding MOH and previous headache were collected: duration, pain location (frontal, temporal, parietal, or occipital), lateralization (unilateral or diffuse), character (dull or pulsating pain), pain intensity (using a numerical pain assessment scale), presence of associated symptoms and signs (nausea/vomiting, photophobia, phonophobia, diplopia, neck and shoulder stiffness, blurred vision, tinnitus, or hypacusis), type of analgesic therapy used, preventive therapy, frequency of using this therapy (number of days per month), and therapy effectiveness (assessment of pain intensity reduction and associated symptoms). We have previously reported detailed data regarding all headache characteristics of the present cohort.\textsuperscript{15}

**Instruments**

All tests were applied at the time of diagnosis (MOH group) or when consent to participate in the study had been provided (CG). The Ruminative Thought Style Questionnaire (RTS) represents a psychometrically sound measure of the general tendency to ruminate. The RTS consists of 20 items that measure a global style that is independent of context, time direction, and valence of affect, by including statements such as “I find myself reliving events again and again” and “When I am looking forward to an exciting event, thoughts of it interfere with what I am working on.” Respondents rate each item on how well it describes their situation using a Likert scale from 1 (not at all) to 7 (very well).\textsuperscript{16} Previous research has shown that the RTS had a high internal consistency (α=0.92) and a high test–retest reliability (0.87) in Serbian respondents.\textsuperscript{17} The Depression Anxiety Stress Scales (DASS) was used to assess depression, anxiety, and stress in the present study. The patient is scored as follows based on their answers to 42 ques-
tions for the previous week: 0 (did not apply to me at all), 1 (applies to me to some degree or for some of the time), 2 (applied to me to a considerable degree or for a high proportion of the time), and 3 (most accurately describes my feelings). The maximum score on this scale is 42 points for each of the depression, anxiety, and stress items, with normal subjects scoring 0–9, 0–7, and 0–14 points, respectively. Higher scores indicate severe depression (>28), anxiety (>20), and stress (>34), with values between high and normal classified as mild or moderate. The DASS had adequate reliability, with internal consistency usually ranging from 0.80 to 0.95, also for testing in the Serbian population. 

The impact of headache on the activities of daily living was assessed using version 1.1 of the Headache Impact Test-6 (HIT-6). HIT-6 is a tool used to measure the impact of headaches on the abilities to function in a job, at school, at home, and in social situations. The patient is scored as follows based on the abilities to function in a job, at school, at home, and in social situations. The patient is scored as follows based on their answers to six questions: 6 (never), 8 (often), 10 (some-times), 11 (very often), and 13 (always). The total score ranges from 36 to 78, with higher scores indicating a greater impact of headache on the quality of life. Scores of 60 or more indicate that headaches are having a very severe impact on the quality of life in terms of family, work, school, or social activities.

Statistical analyses
No power calculations were conducted to determine the sample size required for this study. Data are presented as mean± standard-deviation (range) values or as counts and percentages. The distribution of the values obtained for each of the examined parameters was determined using the Kolmogorov-Smirnov test, and then the appropriate test was applied for the statistical analysis (unpaired Student’s t-test, Mann-Whitney test, or Kruskal-Wallis test). The chi-square test or Fisher’s test was used to analyze categorical data. Correlation coefficients were calculated to quantify the associations between rumination and parameters of psychological distress.

An exploratory logistic regression analysis using the enter method was conducted to further assess the significant associations between rumination, depression, anxiety, stress, and demographic and clinical characteristics. Variables for which \( p < 0.10 \) in these analyses were retained for inclusion in the multivariate model (backward Wald method). Logistic and linear regression were performed as part of the recommended steps for estimating mediating effects. The first step was estimating the relationship between rumination (with the independent variable being the significance of rumination for the occurrence of MOH, tested in the multivariate analysis) and MOH (dependent variable). The next step involved estimating the relationship between rumination (independent variable) and anxiety (with the potential mediator being the significance of anxiety for the occurrence of MOH, tested in the multivariate analysis). The third step involved estimating the relationship between MOH (dependent variable) and anxiety (mediator). In the last step, the effect of rumination on MOH controlled by anxiety as a potential mediator was estimated.

Mediating effects were estimated based on following assumptions: the relationship between the independent and dependent variables should be significant, as well as coefficients in the second and third steps. The relationship between the independent and dependent variables with a mediator in the model should be less significant or not significant compared with in the first step (partial mediation). The Hosmer-Lemeshow test was performed for estimating the calibration ability in the models. A complete case analysis was performed. Statistical significance was defined as \( p < 0.05 \). All statistical analyses were performed using R software (version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS
The study included 164 subjects (33 males and 131 females): 83 patients (11 males and 72 females) in the MOH group and 81 subjects (22 males and 59 females) in the CG. The study subjects were aged 40.2±11.9 years (range 18–71 years). Among 95 subjects who met the inclusion criteria for enrollment in the CG, 14 (14.7%) were excluded due to unwillingness to participate in this study. The age and sex distributions of these excluded subjects did not differ from those in the CG (Fisher’s test, \( p = 0.18 \); chi-square test, \( p = 0.21 \)). During the study period, 982 patients were examined in the Headache Center, 89 of whom were diagnosed with MOH for the first time. We excluded six of the patients due to their unwillingness to participate in this study. The age and sex distributions of the excluded patients did not differ from those in the MOH group (Fisher’s test, \( p = 0.12 \); chi-square test, \( p = 0.15 \)). We have previously reported data regarding the MOH characteristics of the included patients.

The general characteristics of the MOH patients and CG subjects are listed in Table 1. There were significant intergroup differences in the proportion of females (\( p = 0.043 \)), education level (\( p < 0.001 \)), marital status (\( p = 0.003 \)), alcohol consumption (\( p = 0.037 \)), and physical activity (\( p < 0.001 \)). The degrees of rumination, depression, anxiety, and stress were significantly higher in the MOH group (\( p < 0.001 \) for all parameters).

In the MOH group, the degree of rumination was significantly higher in females (\( p = 0.038 \)) and in persons with comorbidities (\( p = 0.008 \)) (Table 2). In the CG, the degree of rumination did not differ significantly with the examined demographic
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The ruminative thought style was more pronounced in MOH patients than in healthy people regardless of age, sex, and place of residence; and in patients with higher education and in those who were married, divorced, or unmarried; and these findings were independent of working status, smoking status, alcohol consumption, consumption of caffeine, and physical activity (Table 2).

There were significant direct correlations between rumination and depression ($r=0.473$, $p<0.001$), anxiety ($r=0.557$, $p<0.001$), and stress ($r=0.474$, $p<0.001$) in MOH subjects, and also in the CG ($r=0.311$, $p=0.005$; $r=0.322$, $p=0.003$; and $r=0.303$, $p=0.005$; respectively) (Table 3).

The degree of rumination was significantly higher in patients receiving combination analgesic therapy ($p=0.015$). No other significant differences were observed with respect to the characteristics of MOH and previous chronic headaches (Table 4).

Univariate analyses identified the following significant risk factors for MOH occurrence: rumination [odds ratio (OR)=1.14, $p<0.001$], sex (OR=2.44, $p=0.029$), marital status (OR=3.19, $p<0.001$), no higher education (OR=0.33, $p=0.001$), alcohol consumption (OR=3.44, $p=0.040$), physical activity (OR=4.69, $p<0.001$), depression (OR=1.14, $p<0.001$), anxiety (OR=1.21, $p<0.001$), and stress (OR=1.17, $p<0.001$). These risk factors were included in a multivariate logistic regression analysis, which identified rumination (OR=1.12, $p<0.001$) and anxiety (OR=1.09, $p=0.039$) as significant risk factors (Table 5).

The mediation analysis revealed that rumination was positively associated with anxiety ($\beta=0.23$, $p<0.001$), which in turn was positively related to MOH ($\beta=0.09$, $p=0.032$). This pattern

### Table 1. General characteristics of the study patients

|                                  | MOH (n=83) | CG (n=81) | p     |
|----------------------------------|------------|-----------|-------|
| **Sociodemographic data**        |            |           |       |
| Sex                              |            |           | 0.043 |
| Male                             | 11 (13.3)  | 22 (27.2) |       |
| Female                           | 72 (86.7)  | 59 (72.8) |       |
| Age                              | 40.54±11.58| 39.94±12.36| 0.747 |
| **Residence**                    |            |           | 0.470 |
| City                             | 65 (78.3)  | 68 (84.0) |       |
| Village                          | 18 (21.7)  | 13 (16.0) |       |
| **Education**                    |            |           | <0.001|
| Elementary school                | 6 (7.2)    | 0 (0.0)   |       |
| High school                      | 44 (53.0)  | 27 (33.3) |       |
| College                          | 33 (39.8)  | 54 (66.7) |       |
| **Marriage status**              |            |           | 0.003 |
| Married                          | 57 (68.7)  | 33 (40.7) |       |
| Divorced                         | 7 (8.4)    | 13 (16.0) |       |
| Widower                          | 1 (1.2)    | 5 (6.2)   |       |
| Unmarried                        | 18 (21.7)  | 30 (37.0) |       |
| **Children**                     |            |           | 0.813 |
| 0                                | 21 (25.3)  | 24 (29.6) |       |
| 1–2                              | 56 (67.5)  | 52 (64.2) |       |
| ≥3                               | 6 (7.2)    | 5 (6.2)   |       |
| **Family members**               |            |           | 0.670 |
| Family members                   | 3.39±1.05  | 3.27±1.18 |       |
| **Working status**               |            |           | 0.591 |
| Work                             | 55 (63.3)  | 56 (69.1) |       |
| Doesn’t work                     | 25 (30.1)  | 24 (29.6) |       |
| Retired                          | 3 (3.6)    | 1 (1.2)   |       |
| **Medical data and habits**      |            |           |       |
| Previous chronic headache*       |            |           |       |
| Migraine (with/without aura)     | 53 (63.9)  | -         | -     |
| Tension type headache            | 21 (25.3)  | -         | -     |
| Secondary headache               | 9 (10.8)   | -         | -     |
| **Comorbidities**                |            |           |       |
| Yes                              | 36 (43.4)  | -         | -     |
| No                               | 47 (56.6)  | -         |       |
| **Type of comorbidities**        |            |           |       |
| Endocrinological                 | 7 (8.4)    | -         | -     |
| Psychiatric                      | 2 (2.1)    | -         | -     |
| Neurological                     | 1 (1.2)    | -         | -     |
| Cardiovascular                   | 10 (12.0)  | -         | -     |
| Pulmonological                   | 7 (8.4)    | -         | -     |
| Rheumatological                  | 9 (10.8)   | -         | -     |
| **Smoking**                      |            |           | 0.722 |
| Yes                              | 34 (41.0)  | 30 (37.0) |       |
| No                               | 49 (59.0)  | 51 (63.0) |       |
| **Duration (years)**             | 7.54±11.13 | 7.78±11.13| 0.850 |
| **n of cigarettes/day**          | 5.42±7.74  | 5.46±7.77 | 0.826 |
| Characteristics         | MOH (n=83) | CG (n=81) | p  |
|-------------------------|------------|-----------|----|
|                         | n          | Ruminations | n | Ruminations |    |
| Age (years)             |            |            |    |
| <40                     | 44         | 90.73±23.18 | 45 | 57.29±12.66 | <0.001 |
| ≥40                     | 39         | 98.33±26.14 | 36 | 56.67±12.83 | <0.001 |
| p-value                 | 0.180      | 0.962      |    |
| Sex                     |            |            |    |
| Male                    | 11         | 81.64±20.83 | 22 | 59.82±9.96  | <0.001 |
| Female                  | 72         | 96.24±24.87 | 59 | 55.97±13.45 | <0.001 |
| p-value                 | 0.038      | 0.302      |    |
| Residence               |            |            |    |
| City                    | 65         | 93.00±23.84 | 68 | 56.10±13.22 | <0.001 |
| Village                 | 18         | 99.00±28.09 | 13 | 61.77±7.95  | 0.001 |
| p-value                 | 0.323      | 0.111      |    |
| Education               |            |            |    |
| Elementary school       | 6          | 93.67±26.45 | -  | -           |    |
| High school             | 44         | 97.52±23.96 | 27 | 60.37±9.44  | <0.001 |
| College                 | 33         | 90.12±25.65 | 54 | 55.33±13.77 | <0.001 |
| p-value                 | 0.518      | 0.131      |    |
| Marriage status         |            |            |    |
| Married                 | 57         | 95.67±25.03 | 33 | 55.88±15.32 | <0.001 |
| Divorced                | 7          | 91.57±30.22 | 13 | 54.69±10.32 | 0.003 |
| Widower                 | 1          | 122.00      | 5  | 56.00±7.45  | 0.333 |
| Unmarried               | 18         | 89.50±22.18 | 30 | 59.43±11.01 | <0.001 |
| p-value                 | 0.561      | 0.429      |    |
| Working status          |            |            |    |
| Work                    | 55         | 92.89±24.77 | 56 | 56.20±13.22 | <0.001 |
| Doesn’t work            | 25         | 95.28±25.40 | 24 | 59.17±11.46 | <0.001 |
| Retired                 | 3          | 112.00±17.32 | 1  | 51.00      | 0.500 |
| p-value                 | 0.330      | 0.586      |    |
| Comorbidities           |            |            |    |
| Yes                     | 36         | 102.56±25.03 | -  | -           |    |
| No                      | 47         | 87.98±22.85 | -  | -           |    |
| p-value                 | 0.008      | -          |    |
| Type of comorbidities   |            |            |    |
| Cardiovascular          | 10         | 108.20±20.76 | -  | -           |    |
| Pulmonary               | 7          | 107.14±27.82 | -  | -           |    |
| Rheumatological         | 9          | 107.33±23.01 | -  | -           |    |
| Endocrinological        | 7          | 85.71±31.54 | -  | -           |    |
| Neurological+psychiatric| 3          | 98.00±15.62 | -  | -           |    |
| p-value                 | 0.578      | -          |    |
| Smoking                 |            |            |    |
| Yes                     | 34         | 97.15±22.14 | 30 | 55.90±12.37 | <0.001 |
| No                      | 48         | 92.33±26.47 | 51 | 57.67±12.90 | <0.001 |
| p-value                 | 0.459      | 0.433      |    |
| Alcohol use             |            |            |    |
| Yes daily or often (several times during the week) | 4 | 82.75±26.68 | 12 | 58.67±13.66 | 0.013 |
| No                      | 79         | 94.88±24.71 | 69 | 56.72±11.62 | <0.001 |
| p-value                 | 0.283      | 0.852      |    |
yields an estimate of the indirect effect of rumination through anxiety of 0.020, which was a significant indirect association because its 95% confidence interval (0.004–0.041) did not include zero. Along with the indirect effect through anxiety, a direct association of rumination with MOH was found (β=0.12, \( p<0.001 \)). The total effect was calculated as the sum of the direct (0.12) and indirect (0.02) associations; that is, 0.14. Hence, around 86% [i.e., 100%−{(0.02)/(0.02+0.12)]×100%] of the total association between rumination and MOH was attributable to a direct association, and the remaining 14% of the total association was attributable to an indirect pathway via anxiety (Fig. 1).

### DISCUSSION

This study found that the degree of rumination was higher in patients with MOH than in the CG, and higher in females, patients with comorbidities, and those who overuse combined analgesic therapy among the patients with MOH. In both the MOH group and the CG, the degree of rumination was directly correlated with depression, anxiety, and stress. Rumination and anxiety have been linked to MOH. The analysis of the present mediation model showed that the connection between rumination and MOH was mainly direct (around 86%), with a smaller additional influence of anxiety as a mediator (14%).

The present findings show that patients with MOH have a higher degree of rumination. Neurovisualization studies have analyzed the existence of a neuroanatomical substrate of the association of different pain catastrophizing dimensions, including also rumination and MOH. These whole-brain volumetric and resting-state functional connectivity analyses found that the somatosensory cortex, supramarginal gyrus, and basal ganglia are involved in the association between rumination and MOH. This suggests the existence of a specific structural and functional neuroanatomical pattern in the association between rumination and MOH.24 Some other studies examining the relationships between pain catastrophizing level, sensory processing patterns, and headache severity in adolescents with episodic migraine have indicated that elevated rumination is correlated with a higher severity of migraine pain. They also indicate a higher pain catastrophizing level in migraine patients than in healthy controls, as also seen in enhanced rumination.25 A study examining both the independent and interactive effects of headache and self-regulatory processes on daily positive and negative affects revealed a direct link between rumination and headache.26

Mindfulness-based cognitive therapy and quality-of-life-based therapy have been shown to significantly improve rumination in patients with migraine, with these changes underlying mechanisms for improving headache and the impact of headache on the quality of life.14 Those authors concluded that these two types of therapy are equally effective in reducing rumination levels and improving headaches.27 A large study that evaluated the relationship between rumination and pain-related outcomes found that rumination was associated with outcome measures, which was accounted for by pain severity, magnification, or helplessness.28

The present study found that the degree of rumination was higher among MOH patients, females, patients with comorbidities, and those who overuse combination analgesic ther-

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**Table 2. Effects of different parameters on rumination in the MOH group and the CG (continued)**

| Characteristics | MOH (n=83) | CG (n=81) | \( p \) |
|-----------------|-----------|-----------|--------|
| **Caffeine use** |           |           |        |
| Yes (more than 3 cups of coffee per day) | 74 | 94.40±25.23 | 70 | 57.86±11.71 | <0.001 |
| No | 9 | 85.22±19.33 | 11 | 51.64±17.30 | <0.001 |
| **p-value** | 0.218 | 0.403 |
| **Physical activity** |           |           |        |
| Yes (several times during the week) | 8 | 87.50±23.96 | 27 | 56.89±12.70 | <0.001 |
| No | 75 | 95.03±24.89 | 54 | 57.07±12.75 | <0.001 |
| **p-value** | 0.312 | 0.673 |

Data are presented as mean±standard deviation unless otherwise indicated. No differences were observed comparing rumination in MOH vs. CG regarding number of children or family number (data are not shown).

CG: control group, MOH: medication overuse headache.

**Table 3. Correlations of rumination with depression, anxiety, and stress**

|          | MOH  | CG  |
|----------|------|-----|
|          | \( r \) | \( p \) | \( r \) | \( p \) |
| **Depression** | 0.473 | <0.001 | 0.311 | 0.005 |
| **Anxiety** | 0.557 | <0.001 | 0.322 | 0.003 |
| **Stress** | 0.474 | <0.001 | 0.303 | 0.005 |

CG: control group, MOH: medication overuse headache, \( r \): correlation coefficient.
Table 4. Rumination regarding MOH and characteristics of previous chronic headache

| MOH                                      | n   | Rumination | p   |
|------------------------------------------|-----|------------|-----|
| **Pain quality**                         |     |            |     |
| Dull                                     | 41  | 93.85±22.85| 0.888|
| Sharp                                    | 42  | 94.74±26.76|      |
| Localization                             | 58  | 0.507      |      |
| **Frontal**                              |     |            |     |
| 14                                       | 91.14±26.19 |          |
| **Occipital**                            |     |            |     |
| 5                                        | 77.20±16.10 |          |
| **Parietal**                             |     |            |     |
| 10                                       | 97.90±29.13 |          |
| **Temporal**                             |     |            |     |
| 54                                       | 96.04±24.10 |          |
| **Lateralization**                       |     |            |     |
| Bilaterally                              | 47  | 91.77±26.53 | 0.238|
| Unilaterally                             | 36  | 97.61±22.17 |      |
| **Symptoms and signs**                   |     |            |     |
| Nausea/vomiting                          | 4   | 81.50±17.06 | 0.291|
| Phosphobia/photophobia                   | 1   | 121.00     |      |
| **Stiffness of neck and shoulders**      |     |            |     |
| 71                                       | 93.96±25.45 |          |
| **Exacerbation on effort**               |     |            |     |
| 7                                        | 104.00±18.34 |         |
| **Type of symptomatic therapy**          |     |            | 0.015|
| Combined analgetics                      | 44  | 100.43±23.54|      |
| NSAIL/metamisol/acetaminophen            | 39  | 87.38±24.57 |      |
| **Efficacy of symptomatic therapy**      |     |            | 0.281|
| No                                       | 18  | 99.56±17.24 |      |
| Partially                                | 65  | 92.85±26.40 |      |
| **Previous chronic headache**            |     |            | 0.690|
| Migraine with/without aura               | 53  | 95.68±25.74 |      |
| Tension type headache                    | 21  | 90.62±24.92 |      |
| Secondary headache                       | 9   | 94.78±19.43 |      |
| **Type of symptomatic therapy**          |     |            | 0.330|
| Combined analgetics                      | 30  | 98.73±22.94 |      |
| NSAIL/Metamisol/Acetaminophen            | 41  | 90.32±25.26 |      |
| Triptans                                 | 12  | 96.83±27.27 |      |
| **Efficacy of symptomatic therapy**      |     |            | 0.444|
| Yes                                      | 59  | 93.90±22.33 |      |
| No                                       | 6   | 84.17±32.57 |      |
| Partially                                | 18  | 99.00±29.74 |      |
| **Used prophylactic pharmacotherapy**    |     |            | 0.672|
| Tricyclic antidepressants                 | 69  | 94.71±24.13 |      |
| Anticonvulsants                          | 3   | 81.30±22.46 |      |
| None                                     | 11  | 95.27±30.03 |      |
| **Used prophylactic nonpharmacotherapy** |     |            | 0.699|
| None                                     | 81  | 94.15±25.05 |      |
| Acupuncture/yoga/etc.                    | 2   | 100.50±0.71 |      |

Data are presented as mean±standard deviation unless otherwise indicated.

*Pain reduction >50% within 2 h of using symptomatic therapy, †>8 headache days per months for at least three last months (according to ICHD-3), based on patients self-reporting.

MOH: medication-overuse headache.
Rumination and Medication-Overuse Headache

The limitations of this study include 1) it being conducted in a single specialized center, 2) the required sample size of the examined cohorts not being calculated, 3) the study design preventing examinations of causality, and 4) difficulties in performing sensitivity analyses of the mediation models. However, the authors firmly believe that their strict methodological approaches reduced bias and increased the scientific validity of this research. Knowledge of significant associations between rumination, anxiety, and MOH may be key to understanding the pathophysiology of MOH, since psychological and personality traits are linked to MOH. These results will contribute to the development of additional and alternative psychological interventions aimed at preventing MOH in selected patients and providing them with better treatments.

In conclusion, the main findings of this study were that rumination and anxiety are significantly associated with MOH, and that the connection between rumination and MOH is largely direct, and to a lesser extent is mediated by anxiety. Psychological strategies aimed at decreasing ruminative responses and anxiety could be useful in preventing MOH in selected patients.

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Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

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