



The Ruminative Thought Style with Associated Anxiety Influences the Occurrence of Medication-Overuse Headache

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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 \pm 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.¹⁰⁻¹³ It has been shown that ruminative thoughts in response to painful experiences intensify psychological distress and reduce the problem-solving capability.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 health-care 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.¹ 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.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).¹⁶ Previous research has shown that the RTS had a high internal consistency ($\alpha=0.92$) and a high test-retest reliability (0.87) in Serbian respondents.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.¹⁸ The DASS had adequate reliability, with internal consistency usually ranging from 0.80 to 0.95, also for testing in the Serbian population.^{19–21}

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 their answers to six questions: 6 (never), 8 (often), 10 (sometimes), 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.²²

Statistical analyses

No power calculations were conducted to determine the sample size required for this study. Data are presented as mean \pm 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.²³ 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.¹⁵

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

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	3.39±1.05	3.27±1.18	0.670
Working status			0.591
Work	55 (63)	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)	-	
Pulmological	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

Table 1. General characteristics of the study patients (continued)

	MOH (n=83)	CG (n=81)	p
Alcohol use daily or often (several times during the week)	4 (4.8)	12 (14.8)	0.037
Caffeine use (more than 3 cups of coffee per day)	74 (89.2)	70 (86.4)	0.767
Physical activity (several times during the week)	8 (9.6)	27 (33.3)	<0.001
Values of measured outcomes			
Rumination	94.30±24.76	57.01±12.65	<0.001
Depression	14.86±10.96	5.78±5.97	<0.001
Anxiety	16.48±9.40	6.53±5.05	<0.001
Stress	22.99±10.11	11.81±6.84	<0.001
HIT-6 (for MOH)	65.39±5.45	-	-

Data are presented as n (%) or mean±standard deviation.

*>8 headache days per months for at least three last months (according to ICHD-3¹), based on patients self-reporting.

CG: control group, HIT-6: headache impact test, MOH: medication-overuse headache.

and clinical parameters. 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 2. Effects of different parameters on rumination in the MOH group and the CG

Characteristics	MOH (n=83)		CG (n=81)		p
	n	Rumination	n	Rumination	
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	-	-	
Pulmological	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	49	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	

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

Characteristics	MOH (n=83)		CG (n=81)		p
	n	Rumination	n	Rumination	
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

	Rumination			
	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.

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 ($\beta=0.12, p<0.001$). 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., $100\% - [0.02/(0.02+0.12)] \times 100\%$] 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 me-

diator (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-

Table 4. Rumination regarding MOH and characteristics of previous chronic headache

	<i>n</i>	Rumination	<i>p</i>
MOH			
Pain quality			0.888
Dull	41	93.85±22.85	
Sharp	42	94.74±26.76	
Localization			0.307
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			0.238
Bilaterally	47	91.77±26.53	
Unilaterally	36	97.61±22.17	
Symptoms and signs			0.391
Nausea/vomiting	4	81.50±17.06	
Phonophobia/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	
NSAID/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	
NSAID/Metamisols/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	81.33±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.

apy. Previous neuroimaging, genetic, and neurobiological studies support the existence of common pathophysiological features of dependence and MOH, and suggest a link between them.²⁹ To our knowledge, the association between rumination and the type of analgesic therapy that is overused has not been examined, and so results are lacking that could be useful for comparison with our findings on the association between rumination and the overuse of combination analgesic therapy. We consider this issue important because it could be useful for developing a psychological treatment strategy in managing patients with MOH by treating dependence.

In this study, the degree of rumination was directly correlated with depression, anxiety, and stress in both the MOH group and the CG. It was previously shown that depression, anxiety, and stress are comorbid with MOH.^{15,30} These associations are supported by the withdrawal of overused therapy leading to significant improvements in depression and anxiety, as well as depression and anxiety being associated with a poor outcome in terms of headache frequency.³¹ Anxiety, depressive symptoms, somatization, and catastrophizing pain are significantly more prevalent in chronic types of headache such as MOH than in healthy individuals and patients with other chronic pain conditions such as chronic low-back pain.³² An examination of rumination as an explanatory factor in the relationship between pain and anxiety and depressive symptoms in a large sample of students with pain indicated that rumination explains the relationships of pain with depressive and social anxiety symptoms, and also anxious arousal symptoms.³³ Another study indicated that mindfulness-based stress reduction can improve the quality of life and be useful in developing strategies for coping with pain in patients with chronic headache.³⁴

We found that rumination and anxiety are significantly linked to MOH. The analysis of the mediation showed that the connection between rumination and MOH was largely direct (around 86%), and additionally influenced by anxiety as a mediator (14%). It was found previously that rumination fully mediated the relationship between neuroticism and somatic complaints.³⁵ It has also been shown previously that a ruminative response style mediates the relationship between migraine and elevated psychological distress.³⁶ A ruminative cognitive style was both directly associated with health anxiety and also indirectly associated with health anxiety via its strong relationship with negative affect.¹⁴ On the other hand, voxel-based morphometric and structural magnetic resonance imaging findings have shown dysfunction of antinociceptive systems in MOH, which is mainly influenced by anxiety in MOH patients.³⁷ It has been further documented that MOH patients constitute a highly disabled group in which anxiety and depression are important comorbidities.³⁸ The associa-

Table 5. Risk factors for medication-overuse headache

	Univariate			Multivariable		
	OR	95% CI	p	OR	95% CI	p
Rumination	1.14	1.09–1.19	<0.001	1.123	1.071–1.178	<0.001
Sex	2.44	1.10–5.44	0.029	0.874	0.261–2.929	0.827
Age	1.00	0.98–1.03	0.745			
Married vs. single	3.19	1.68–6.06	<0.001	1.756	0.618–4.995	0.291
City vs. village	1.45	0.66–3.19	0.358			
College	0.33	0.17–0.62	0.001	0.810	0.2888–2.279	0.689
Number of children	1.13	0.74–1.73	0.569			
Smoking	0.85	0.45–1.59	0.606			
Duration of smoking	0.99	0.97–1.03	0.894			
Alcohol	3.44	1.06–11.14	0.040	0.867	0.185–4.061	0.857
Caffeine	0.77	0.30–1.98	0.593			
Physical activity	4.69	1.98–11.11	<0.001	2.438	0.661–8.968	0.181
Depression	1.14	1.08–1.20	<0.001			
Anxiety	1.21	1.14–1.29	<0.001	1.091	1.005–1.185	0.039
Stress	1.17	1.11–1.23	<0.001			

CI: confidence interval, OR: odds ratio.

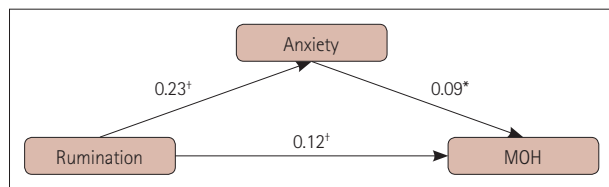


Fig. 1. Direct effect of rumination and mediating effect of anxiety in connection with medication-overuse headache (MOH) (* $p < 0.05$, $^{\dagger}p < 0.001$).

tion between rumination and stress and the effect of mindfulness-based stress reduction have been demonstrated in a population of patients living with cancer, where decreases in rumination had a beneficial effect on depressive symptoms.³⁹ It has been concluded that changing maladaptive psychophysiological responses (including rumination) in addition to pharmacotherapy is a promising approach for reducing the headache frequency and analgesic intake in MOH.⁴⁰

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.

Author Contributions

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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