

The role of stress and psychiatric comorbidities as targets of non-pharmacological therapeutic approaches for migraine

Ruolo dello stress e delle comorbidità psichiatriche come target degli approcci terapeutici non farmacologici per l'emicrania

CORINNA PANCHERI¹, ANNALISA MARAONE¹, VALENTINA ROSELLI¹, MARTA ALTIERI¹, VITTORIO DI PIERO¹, MASSIMO BIONDI¹, MASSIMO PASQUINI¹, LORENZO TARSITANI^{1*}

*E-mail: lorenzo.tarsitani@uniroma1.it

¹Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Italy

SUMMARY. This narrative review addresses the interconnections among stress, mental disorders and migraine with a specific focus on non-pharmacological interventions that may be effective in improving both migraine and the psychiatric comorbidity. Migraine is often comorbid with depression, anxiety, personality disorders, and sleep disorders. Subjective stress and stressors are common triggers for migraine attacks and are risk factors for chronification, whilst mental disorders and stress responses are closely linked in a bidirectional relation. Recent studies show that psychiatric comorbidity is associated with migraine severity, worse outcomes, increased disability and reduce quality of life. Numerous studies on non-pharmacological interventions for migraine were published and behavioural treatments included biofeedback, cognitive-behavioural therapy, relaxation training, stress management and brief psychodynamic psychotherapy. Taken together, psychological interventions proved to be effective in migraine treatment and a combination of pharmacological and psychological treatment appear to be more effective than either medication or psychotherapy alone. Non-pharmacological interventions effectiveness should be due to the improvement of migraine, stress-related vulnerability and mental disorders together and the combined treatment could prevent the chronification circuit of migraine. Well-designed long-term studies are needed to clarify comparative effectiveness of non-pharmacological techniques in the treatment and the prevention of migraine.

KEY WORDS: migraine, comorbidity, mental disorders, psychiatric disorders, psychotherapy.

RIASSUNTO. Lo scopo di questa revisione è quello di analizzare la correlazione tra stress, disturbi mentali ed emicrania, con un focus specifico sugli interventi non farmacologici, che possono essere efficaci nel migliorare sia l'emicrania sia la comorbidità psichiatrica. L'emicrania è stata spesso associata a depressione, ansia, disturbi della personalità e disturbi del sonno. Lo stress soggettivo e gli stressor sono elementi scatenanti comuni per gli attacchi di emicrania e, inoltre, sono fattori di rischio per la sua cronicizzazione, mentre i disturbi mentali e le risposte allo stress sono strettamente collegati all'emicrania in una relazione bidirezionale. Studi recenti mostrano che la comorbidità psichiatrica è associata a una maggiore gravità dell'emicrania, a un peggiore outcome, all'aumento della disabilità e alla riduzione della qualità della vita. Gli interventi non farmacologici e i trattamenti comportamentali come il biofeedback, la terapia cognitivo-comportamentale, le tecniche di rilassamento, la gestione dello stress e la psicoterapia psicodinamica breve si sono dimostrati efficaci nel trattamento dell'emicrania. Inoltre, la terapia combinata, farmacologica e non, sembra essere più efficace della sola farmacoterapia o psicoterapia. Gli interventi non farmacologici nei pazienti con emicrania sembrano favorire il miglioramento dei sintomi e la riduzione della vulnerabilità allo stress e ai disturbi mentali e, il trattamento combinato, potrebbe prevenire il meccanismo di cronicizzazione dell'emicrania. Sono necessari studi a lungo termine per chiarire l'efficacia comparativa delle tecniche non farmacologiche nel trattamento e nella prevenzione dell'emicrania.

PAROLE CHIAVE: emicrania, comorbidità, disordini mentali, disturbi psichiatrici, psicoterapia.

INTRODUCTION

People suffering from psychiatric disorders and emotional difficulties may turn to various providers to ask for help, especially mental health specialists¹. In mental health settings, psychotherapy is one of the main therapeutic options available for patients suffering from a variety of common and mild or moderate mental disorders. Psychological interventions are the only indicated options for personality disorders. Also, psychotherapy is often offered to persons seeking help for emotional distress correlated with stressful somatic

conditions such as migraine. The scientific literature shows an association between migraine and several psychiatric conditions that may lead people to seek psychotherapeutic help, such as stress-related emotional difficulties, personality disorders, depressive and anxiety disorders, bipolar spectrum disorders and sleep disorders^{2,3}. Furthermore, many studies developed hypotheses on the contribution of depression and anxiety to the chronification of migraine, increasing the interest in psychological integrative solutions⁴⁻⁷. This paper aims at presenting the interconnections between psychiatric disorders and migraine with a specific focus on non-pharma-

The role of stress and psychiatric comorbidities as targets of non-pharmacological therapeutic approaches for migraine

ological interventions that may be effective in improving both migraine and the psychiatric comorbidity and to prevent the so called chronification circuit.

A non-systematic search was performed using MEDLINE/PubMed database with the following key words: (migraine OR headache) AND (depression OR anxiety OR personality disorder); (migraine OR headache) AND (sleep problems OR sleep disorder); (migraine OR headache) AND psych* AND stress; (migraine OR headache) AND (psychological intervention OR psychological treatment OR non-pharmacological intervention OR psychotherapy). In the Table 1, inclusion criteria for papers selection are reported.

MIGRAINE AND PSYCHIATRIC COMORBIDITY

Approximately 12% of the general population suffers from migraine⁸ and about 9% of people suffering from episodic migraine have chronic migraine⁹. Several studies suggest that migraine is more than two times more frequent in women than in men^{10,11}. Moreover, women have a greater risk to develop disability¹² as well as a greater risk of evolution from episodic to chronic migraine¹³.

The association between migraine and psychiatric disorders has been described in both clinical and community based populations. Many studies confirmed the presence of a high co-occurrence between depression, anxiety, personality disorders, sleep problems and migraine. Table 1 summarizes main studies on this comorbidity. Patients with migraine presented with a significantly greater number of comorbid psychiatric disorders than patients without migraine¹⁴. Epidemiologic studies also report a female tendency to development both depression and anxiety disorders in migraineurs with a prevalence twice in women than men^{15,16}. Moreover some studies demonstrated that psychiatric comorbidities are more prevalent in chronic migraine than in episodic migraine^{9,17-19}.

The presence of a psychiatric comorbidity seems to enhance migraine triggers susceptibility and the number of headaches/month²⁰, as well as to increase disability and to reduce quality of life (QoL). Moreover, patients with comorbid mental disorders and migraine show a worse response to migraine treatment (due especially to low adherence), which can negatively modify long-term outcomes of migraineurs patients^{21,22}.

Patients with migraine and a comorbid mental disorder have worse general health outcomes compared with individuals with one condition^{23,24}.

Concerning depression, the nature of the relation with migraine is not clearly demonstrated, but longitudinal studies suggest a bi-directional relationship. Breslau and colleagues, in three longitudinal studies^{15,25,26}, found similar figures for new onset migraine in subjects with depression and for new onset depression in migraineurs. However, Swartz did not confirm the higher risk of new onset migraine in depressed patients²⁷. A recent review and meta-analysis found that the effects of migraine on depression was equal to OR=1.81 (95% CI=1.20-2.72) in cohort studies, and OR=2.00; 95% CI=1.64-2.43 in cross sectional studies, concluding that migraine can play an important role in increasing the incidence of depression in affected patients²⁸.

Depression was also a significant predictor of onset of chronic migraine in patients with episodic migraine (OR=1.65, 95% CI=1.12-2.45) and the risk of chronic migraine onset increased with depression severity^{6,19}.

Anxiety Disorders too seems to be strongly related to migraine (Table 1) and a factor potentially associated with reduced perception of efficacy with acute treatment, long-term migraine persistence, headache-related disability and with chronic outcomes^{13,29,30}.

Concerning Personality Disorders, recent studies suggest that migraineurs and chronic migraineurs have higher rates of certain personality disorders as compared to individuals without migraine^{31,32} (Table 1). The coexistence of a borderline personality disorder seems associated with more pervasive headache, more migraine-related disability, and an increase difficulty to treat due to a higher prevalence of medication overuse and more unscheduled visits for acute migraine treatment^{33,34}. Although less investigated than borderline personality disorder, avoidant personality disorder and obsessive-compulsive personality disorder, which are classified in a different cluster of personality disorders, have also been associated with migraine and seem to negatively impact migraine treatment, contributing to medication overuse and poorer prognosis^{35,36}. However, literature is scarce and a cause-effect relationship between personality disorders and migraine remains unproven.

Sleep problems are more prevalent in patients with migraine than in the general population³⁷. The association between severe sleep disturbances and migraine seems to be more pronounced for chronic migraine³⁸. Patients with chronic migraine reported shorter nightly sleep times than those with episodic migraine, and were more likely to exhibit trouble falling asleep, staying asleep and sleep triggering headache³⁹. As with depression and anxiety, also for sleep disturbances the relationship with migraines appear bidirectional with pain negatively impacting sleep and vice versa⁴⁰.

ROLE OF THE STRESS AND THE CHRONIFICATION CIRCUIT

Stress is the factor listed most often by migraine sufferers as a trigger for their attacks. Some studies show that 50% to 80% of patients report stress as a trigger factor for their migraine attacks. It has been suggested that acute stress can provoke biological modifications lowering the threshold of susceptibility to a migraine attack⁴¹. Moreover, when behavioural or physiological stressors are frequent and/or severe, allostatic responses can become dysregulated and maladaptive ("allostatic load"), altering the normal response of physiological systems and leading to alterations in brain networks, both functionally and structurally. These effects can lead to abnormal responses to environmental conditions and to the chronification of the disease^{42,43}. The overuse of analgesic medications, might affect allostasis, too⁴⁴. Moreover, it has been well established from the 1970s that stress and psychiatric disorders are extremely related with a bidirectional relationship⁴⁵. Therefore, migraine, stress and psychiatric disorders seem to be tied together, leading patients into a chronification circuit where every condition may provoke or incentivize the other with a final reduction in quality of life and worse outcomes.

(Author, year) ^{reference}	Psychiatric diagnosis	Sample	Psychiatric comorbidity	Results/conclusions
Depressive and/or anxiety disorders				
(Merikangas, 1990) ⁷⁹	PI	N=457	Depression OR (95% CI): 2.2 (1.1-4.8);	Concluded a higher risk of depression and anxiety and depressive disorders in combination.
(Breslau, 1994) ²⁵	PI	N=1007	Depression OR (95% CI): - New-onset migraine 3.5 (2.2-5.6) - New-onset depression 3.6 (2.6-5.2)	Data strongly support clinical observations on migraine-major depression comorbidity.
(Verri, 1998) ⁸⁰	PI DSM-III	N=88	MDD: 25% GAD: 69.3%	Concluded high comorbidity of anxiety and mood disorders in migraineurs.
(Mitsikostas, 1999) ⁸¹	HAM-A and D	N=620 (170 with migraine)	Depressive Disorders OR 7.3 (prevalence 4%)	Higher scores of anxiety and depression in migraineurs compared to healthy controls.
(Breslau, 2000) ¹⁵	PI DSM-IV	N=1287 (536 with migraine)	Depression OR (95% CI): 3.5 (2.6-4.6). - New-onset migraine 2.8, 2.2 to 3.5 - New-onset depression 2.4, 1.8 to 3.0	Different causes may underlie the co-occurrence of major depression in persons with migraine compared with persons with other severe headaches.
(Juang, 2000) ⁸²	MINI	N=261 (152 with migraine)	Depressive Disorders: 46% Anxiety Disorders: 28%	Psychiatric comorbidity, especially MDD and panic disorders, was highly prevalent in patients with migraine.
(Swartz, 2000) ²⁷	PI DSM-III	N=1343 (118 with migraine)	Depression comorbidity OR (95% CI): 3.1, (2.0-4.4) New-onset migraine in depression 0.68 (.02-2.0)	There is a strong cross-sectional relation between depression and migraine, but no association between antecedent depression and incident migraine.
(McWilliams, 2004) ⁸⁴	PI DSM-III	N=3032 (340 with migraine)	Depression OR (95% CI): 2.8 (2.2-3.7) Panic attacks OR (95% CI): 3.6 (2.6-3.0) GAD OR (95% CI): 3.9 (2.5-6)	Strong association between psychiatric disorders and migraine. Association was stronger for anxiety disorders than depression.
(Atasoy, 2005) ³⁵	PI SCID-CV	N=117 (58 with migraine)	Depressive Disorders: 36% Anxiety Disorders: 17% (GAD: 8.6%, Panic 6.9%)	High comorbidity of anxiety and depressive disorders in patients with migraine.
(Senaratne, 2010) ¹⁴	SCID DSM-IV	N=206 (138 with migraine)	Anxiety Disorders: 67% comorbidity with: - MDD/Dysthymia: p=0.008 - GAD/PD: p=0.048	The prevalence of migraine was significantly higher in patients with a diagnosis of PD or MDD/dysthymia compared to other psychiatric disorders.
(Goulart, 2014) ⁸⁵	CIS-R	N=11792 (1261 with migraine)	For daily headaches: MDD OR (95% CI): 6.94 (4.20-11.49) GAD OR (95% CI): 4.0 (2.6-7.0) PD OR (95% CI): 2.1 (0.6-7.1) Mixed anxiety-depressive disorder OR (95% CI): 1.9 (1.1-3.0)	The increase in migraine frequency was associated with progressively higher frequencies of having mood/anxiety disorders.
(Fuller-Thomson, 2017) ⁸⁶	WHO-CIDI	N=21502 (2232 with migraine)	GAD OR (95% CI): 2.46 (2.0-3.0)	GAD is robustly associated with migraine.

(Continued) - Table 1

The role of stress and psychiatric comorbidities as targets of non-pharmacological therapeutic approaches for migraine

(Continued) - Table 1

(Author, year) ^{reference}	Psychiatric diagnosis	Sample	Psychiatric comorbidity	Results/conclusions
Depressive and/or anxiety disorders				
(Dindo, 2017) ⁸⁷	PI DSM-IV TR	N=227 (31 with mi- graine)	MDD OR (95% CI): 3.4 (1.1-10.2) GAD OR (95% CI): 3.0 (1.3-6.8)	A diagnosis of MDD or GAD was associated with significantly increased risk of having migraine. Personality disorders
Personality disorders				
(Wang, 2005) ³⁶	DAPP	N=160 (48 with migraine)	Personality traits (migraineurs vs controls p<0.5): - Submissiveness - Cognitive distortion - Social Avoidence - Self-Harm	Results suggests that mi- graine is comorbid with borderline personality traits, and avoidant per- sonality traits.
(Lake, 2009) ⁸⁸	PI DSM-IV TR	N=267 (226 with CM)	Personality Disorders: 26% - Cluster B: 16% - Cluster C: 12%	Most common personality disorders of which migraineurs are affected are from cluster B and cluster C.
(Manlik, 2012) ⁸⁹	SIDP DSM-III	N=352 (49 with mi- graine)	Personality Disorders OR (95% CI): 3.44 (1.8-6.7) - Passive-aggressive OR (95% CI): 3.18 (1.3-7.8) - Mixed OR (95% CI): 5 (1.5-16.6)	The most notable findings are the association of migraine with passive- aggressive and mixed personality disorders (DSM-III)
(Kayhan, 2016) ³²	SCID-II	N=205 (105 with CM)	Any Personality Disorders 81% OR (95% CI) 0.05 (0.02-0.11)	Most prevalent disorders were Obsessive- compulsive (50.5%), avoidant (19%), dependent (19%), passive-aggressive (13.3%), narcissistic (6.7%), borderline (5.7%), histrionic (5.7%) disorders.

Legend: PI=Psychiatric Interview; HAM-A and D=Hamilton Rating Scale for Anxiety and Depression MDD=Major Depressive Disorder; GAD=Generalized Anxiety Disorder; MINI=Mini-International Neuropsychiatric Interview; HADS=Hospital Anxiety and Depression Scale; CIS-R=Clinical Interview Schedule-Revised; WHO-CIDI=World Health Organization Composite International Diagnostic Interview; PD=Panic Disorder; DAPP=Dimensional Assessment of Personality Pathology; SCID-II=Structured Clinical Interview for DSM IV-TR.

NON-PHARMACOLOGICAL INTERVENTIONS

Due to the high prevalence of psychiatric comorbidity and stress in migraine and the impact of comorbidity on outcomes, in the last decades attention was directed to psychological interventions aimed at addressing both migraine and mental conditions. Following the history of psychosomatic medicine started a century ago⁴⁶, from the '80s studies on psychological treatment of headache and migraine were published and included biofeedback, cognitive-behavioural therapy (CBT), relaxation training, stress management and other techniques⁴⁷. These behavioural therapies have very well-established efficacy for treatment of migraine, as con-

firmed in numerous studies and meta-analyses⁴⁸. Furthermore, the combination of pharmacological treatment and behavioural therapy has been found to be more effective than either medication or behavioural therapy alone⁴⁹⁻⁵¹.

CBT is an important treatment component especially for patients with a comorbid psychiatric conditions⁵². The rationale for the use of CBT in migraine management derives from the observation that the way people cope with everyday stressors can precipitate, exacerbate, or maintain headaches and increase headache-related disability and distress.

Advice to identify and avoid triggers, particularly those related to pathological mental conditions (stress and negative

emotions, anger, lack of sleep or excess of sleep, alcohol abuse etc.)⁵³ as a good means of preventing headaches, has been standard practice for decades. Martin and colleagues recently developed an alternative approach to trigger management called “learning to cope with triggers” (LCT)⁵⁴ consisting in a graduated exposure to selected triggers to promote desensitization. They propose an integrative CBT/LCT approach which aims to enhance the effectiveness of CBT in migraineurs⁵⁵. The same Authors in a randomized controlled trial in patients with comorbid headaches and depression, found that the CBT group improved significantly more than the control group mostly in men than women⁵⁶. Indeed, the latest outcome is in contrast with literature⁵⁷ and it could be associated with a greater tendency to ruminate in females than males⁵⁸. This ruminative response style may increase the risk to develop a persistence depression⁵⁹ and this could explain the gender difference in treatment response⁵⁶. Improvements achieved with treatment were maintained at four month follow-up. Furthermore, advice to avoid triggers altogether may lead to reduced internal locus of control for headaches, with attendant adverse effects on self-efficacy, particularly concerning perceived capacity to cope effectively with triggers⁶⁰.

The self-management model, typically employed in cognitive-behavioural interventions, is very useful in patients with migraine and comorbid psychiatric disorders. This model optimizes medication adherence, effects lifestyle changes, improves functioning, limits disability, teaches way to manage stress and affective distress as well as educates about the role of cognitions and behaviours in health and illness⁶¹.

In recent studies, different forms of CBT in migraineur patients, have shown to be effective not only to manage patients' headache pain, but also on reducing the depressed mood and/or the anxiety symptoms⁶²⁻⁶⁴. Also the biofeedback treatment proved to be effective both on migraine and anxiety and depressive comorbidity^{65,66}. A recent pilot randomized controlled trial showed that biofeedback added to traditional pharmacological therapy in the treatment of medication overuse headache improved outcome in headache frequency, amount of drug intake and active coping with pain, also after 4 months of follow-up⁶⁷. Though more research is needed on the effects of treating comorbid psychiatric disorders on headache outcomes and vice versa, these findings help to demonstrate the bidirectional relationship between depression, anxiety and migraine.

Other “emerging therapies” include: acceptance and commitment therapy (ACT)^{68,69}, mindfulness-based intervention⁷⁰⁻⁷², and behavioural interventions that target comorbid conditions as sleep disturbances^{73,74}. Though existing studies are small, these approaches have produced positive outcomes, particularly in the domains of improving headache-related functioning and affective distress⁷⁵. There is evidence that relaxation techniques, particularly progressive muscle relaxation, and different biofeedback techniques are effective in reducing frequency and severity of migraine⁷⁶.

In a study on patients with medication overuse headaches, short-term psychodynamic psychotherapy added to pharmacological therapy, at 12-month follow-up, was associated with decreased headache frequency and medication intake, a lower relapse rate, and a lower risk of developing chronic migraine, as compare to pharmacotherapy alone⁷⁷. Less studied, brief psychodynamic treatments appear promising in terms of feasibility compared to standard psychodynamic

therapy. Insight oriented approaches could be helpful in decreasing stress-related vulnerability as well as somatization tendencies, potentially leading to long term results. Future studies are needed to demonstrate this hypothesis.

Importantly, all psychological interventions used in migraine proved to be effective in anxiety, depressive and stress-related disorders alone. Hence, the effect in patients with migraine and psychiatric comorbidity should be due to the improvement of migraine, stress-reactions and mental disorders together. In theory, the psychological effect of treatments could also prevent the chronification circuit addressing all conditions involved.

Finally, it is useful to note that the use of psychological techniques in migraineurs with comorbid mental disorders may provide a nonthreatening way to introduce the patient to the process of psychological treatment and thus, to encourage the patient to acknowledge psychological difficulties and accept treatment for psychiatric disorders⁶¹.

From a mental health perspective, non-pharmacological interventions for mental disorders in children and adolescents are highly indicated to improve long-term outcomes and avoid chronicity. However, most studies on migraine with psychiatric comorbidity are on adults. Only 11 trials from 2010 assessed behavioural approaches, mostly CBT, in adolescents or young adults with headache⁷⁸. Two studies involved only patients with chronic migraine and depression or anxiety were considered as a secondary outcome in 4 studies. Non-pharmacological treatments were shown to produce sizeable effects on headache frequency and marked improvements were noted in depressive and anxiety symptoms. Future well-designed studies are necessary to explore the short- and long-term effectiveness of behavioural intervention in adolescents or young adults with migraine and psychiatric comorbidity.

CONCLUSIONS

Comorbid mental disorders, specially anxiety, depressive, and personality disorders are the rule rather than the exception in migraine. Stress-related vulnerability is associated with both migraine and psychiatric conditions. The co-occurrence of these conditions has a great impact on health. Psychological interventions are clearly indicated and effective for mild/moderate mental disorders and stress vulnerability. Several studies showed their effectiveness in patients with migraine, usually added to pharmacological treatment, suggesting a combined action on psychological and somatic symptoms. Future research is needed to better understand long-term effectiveness and to compare different psychological techniques.

Conflict of interests: the authors have no conflict of interests to declare.

REFERENCES

1. Kovess-Masfety V, Alonso J, Brugha TS, et al. Differences in lifetime use of services for mental health problems in six European countries. *Psychiatr Serv* 2007; 58: 213-20.
2. Minen MT, Begasse De Dhaem O, et al. Migraine and its psychiatric comorbidities. *J Neurol Neurosurg Psychiatry* 2016; 87: 741-9.
3. Hamelsky SW, Lipton RB. Psychiatric comorbidity of migraine. *Headache* 2006; 46: 1327-33.

The role of stress and psychiatric comorbidities as targets of non-pharmacological therapeutic approaches for migraine

4. Dodick D. Review of comorbidities and risk factors for the development of migraine complications (infarct and chronic migraine). *Cephalalgia* 2009; 29: 7-14.
5. Scher AI, Midgette LA, Lipton RB. Risk factors for headache chronification. *Headache* 2008; 48: 16-25.
6. Ashina S, Serrano D, Lipton RB, et al. Depression and risk of transformation of episodic to chronic migraine. *J Headache Pain* 2012; 13: 615-24.
7. Diener H-C, Solbach K, Holle D, Gaul C. Integrated care for chronic migraine patients: epidemiology, burden, diagnosis and treatment options. *Clin Med* 2015; 15: 344-50.
8. Yeh WZ, Blizzard L, Taylor BV. What is the actual prevalence of migraine? *Brain Behav* 2018; 8: e00950.
9. Scher AI, Buse DC, Fanning KM, et al. Comorbid pain and migraine chronicity: the chronic migraine epidemiology and outcomes study. *Neurology* 2017; 89: 461-8.
10. IHME. Global Burden of Disease Study 2015 (GBD 2015). Seattle, WA: Institute for Health Metrics and Evaluation, 2016.
11. Finocchi C, Strada L. Sex-related differences in migraine. *Neurol Sci* 2014; 35: 207-13.
12. Stovner L, Hagen K, Jensen R, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007; 27: 193-210.
13. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache* 2008; 48: 1157-68.
14. Senaratne R, Van Ameringen M, Mancini C, Patterson B, Bennett M. The prevalence of migraine headaches in an anxiety disorders clinic sample. *CNS Neurosci Ther* 2010; 16: 76-82.
15. Breslau N, Schultz LR, Stewart WF, Lipton RB, Lucia VC, Welch KM. Headache and major depression: is the association specific to migraine? *Neurology* 2000; 54: 308-13.
16. Vesga-López O, Schneier FR, Wang S, et al. Gender differences in generalized anxiety disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Clin Psychiatry*. 2008; 69: 1606-16.
17. Blumenfeld A, Varon S, Wilcox T, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). *Cephalalgia* 2011; 31: 301-15.
18. Mathew NT, Reuveni U, Perez F. Transformed or evolutive migraine. *Headache* 1987; 27: 102-6.
19. Yalug I, Selekler M, Erdogan A, et al. Correlations between alexithymia and pain severity, depression, and anxiety among patients with chronic and episodic migraine. *Psychiatry Clin Neurosci* 2010; 64: 231-8.
20. Baldacci F, Lucchesi C, Cafalli M, et al. Migraine features in migraineurs with and without anxiety-depression symptoms: a hospital-based study. *Clin Neurol Neurosurg* 2015; 132: 74-8.
21. Hung CI, Wang SJ, Yang CH, Liu CY. The impacts of migraine, anxiety disorders, and chronic depression on quality of life in psychiatric outpatients with major depressive disorder. *J Psychosom Res* 2008; 65: 135-42.
22. Lantéri-Minet M, Radat F, Chautard M-H, Lucas C. Anxiety and depression associated with migraine: influence on migraine subjects' disability and quality of life, and acute migraine management. *Pain* 2005; 118: 319-26.
23. Jette N, Patten S, Williams J, Becker W, Wiebe S. Comorbidity of migraine and psychiatric disorders: a national population-based study. *Headache* 2008; 48: 501-16.
24. Breslau N, Davis GC. Migraine, physical health and psychiatric disorder: a prospective epidemiologic study in young adults. *J Psychiatr Res* 1993; 27: 211-21.
25. Breslau N, Merikangas K, Bowden CL. Comorbidity of migraine and major affective disorders. *Neurology* 1994; 44: S17-22.
26. Breslau N, Lipton RB, Stewart WF, Schultz LR, Welch KMA. Comorbidity of migraine and depression: investigating potential etiology and prognosis. *Neurology* 2003; 60: 1308-12.
27. Swartz KL, Pratt LA, Armenian HK, Lee LC, Eaton WW. Mental disorders and the incidence of migraine headaches in a community sample: results from the Baltimore Epidemiologic Catchment area follow-up study. *Arch Gen Psychiatry* 2000; 57: 945-50.
28. Amiri S, Behnezhad S, Azad E. Migraine headache and depression in adults: a systematic review and meta-analysis. *Neuropsychiatry* 2019; 33: 131-40.
29. Smitherman TA, Penzien DB, Maizels M. Anxiety disorders and migraine intractability and progression. *Curr Pain Headache Rep* 2008; 12: 224-9.
30. Antonaci F, Nappi G, Galli F, Manzoni GC, Calabresi P, Costa A. Migraine and psychiatric comorbidity: a review of clinical findings. *J Headache Pain* 2011; 12: 115-25.
31. Davis RE, Smitherman TA, Baskin SM. Personality traits, personality disorders, and migraine: a review. *Neurol Sci* 2013; 34: 7-10.
32. Kayhan F, Ilik F. Prevalence of personality disorders in patients with chronic migraine. *Compr Psychiatry* 2016; 68: 60-4.
33. Rothrock J, Lopez I, Zweifler R, Address-Rothrock D, Drinkard R, Walters N. Borderline personality disorder and migraine. *Headache* 2007; 47: 22-6.
34. Saper JR, Lake AE. Borderline personality disorder and the chronic headache patient: review and management recommendations. *Headache* 2002; 42: 663-74.
35. Atasoy HT, Atasoy N, Unal AE, Emre U, Sumer M. Psychiatric comorbidity in medication overuse headache patients with pre-existing headache type of episodic tension-type headache. *Eur J Pain* 2005; 9: 285-91.
36. Wang W, Yang T, Zhu H, et al. Disordered personality traits in primary headaches. *Soc Behav Personal Int J* 2005; 33: 495-502.
37. Rains JC, Poceta JS. Headache and sleep disorders: review and clinical implications for headache management. *Headache* 2006; 46: 1344-63.
38. Ødegård SS, Engstrøm M, Sand T, Stovner LJ, Zwart J-A, Hagen K. Associations between sleep disturbance and primary headaches: the third Nord-Trøndelag Health Study. *J Headache Pain* 2010; 11: 197-206.
39. Kelman L, Rains JC. Headache and sleep: examination of sleep patterns and complaints in a large clinical sample of migraineurs. *Headache* 2005; 45: 904-10.
40. Dosi C, Figura M, Ferri R, Bruni O. Sleep and headache. *Semin Pediatr Neurol* 2015; 22: 105-12.
41. Radat F. Stress et migraine. *Rev Neurol* 2013; 169: 406-12.
42. Maleki N, Becerra L, Borsook D. Migraine: maladaptive brain responses to stress. *Headache* 2012; 52: 102-6.
43. Sauro KM, Becker WJ. The stress and migraine interaction. *Headache* 2009; 49: 1378-86.
44. Rainero I, Ferrero M, Rubino E, et al. Endocrine function is altered in chronic migraine patients with medication-overuse. *Headache* 2006; 46: 597-603.
45. Paykel ES. Contribution of life events to causation of psychiatric illness. *Psychol Med* 1978; 8: 245-53.
46. Raginsky BB. Psychosomatic medicine: its history, development and teaching. *Am J Med* 1948; 5: 857-78.
47. Blanchard EB. Psychological treatment of benign headache disorders. *J Consult Clin Psychol* 1992; 60: 537-51.
48. Rains JC, Penzien DB, McCrory DC, Gray RN. Behavioral headache treatment: history, review of the empirical literature, and methodological critique. *Headache* 2005; 45: S92-S109.
49. Matchar DB, Harpole L, Samsa GP, et al. The headache mana-

- gement trial: a randomized study of coordinated care. *Headache* 2008; 48: 1294-310.
50. Powers SW, Kashikar-Zuck SM, Allen JR, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents. *JAMA* 2013; 310: 2622.
 51. Holroyd KA, Cottrell CK, O'Donnell FJ, et al. Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. *BMJ* 2010; 341: c4871.
 52. Lipchik GL, Nash JM. Cognitive-behavioral issues in the treatment and management of chronic daily headache. *Curr Pain Headache Rep* 2002; 6: 473-9.
 53. Andress-Rothrock D, King W, Rothrock J. An analysis of migraine triggers in a clinic-based population. *Headache* 2010; 50: 1366-70.
 54. Martin PR, Reece J, Callan M, et al. Behavioral management of the triggers of recurrent headache: a randomized controlled trial. *Behav Res Ther* 2014; 61: 1-11.
 55. Martin PR, Mackenzie S, Bandarian-Balooch S, et al. Enhancing cognitive-behavioural therapy for recurrent headache: design of a randomised controlled trial. *BMC Neurol* 2014; 14: 233.
 56. Martin PR, Aiello R, Gilson K, Meadows G, Milgrom J, Reece J. Cognitive behavior therapy for comorbid migraine and/or tension-type headache and major depressive disorder: an exploratory randomized controlled trial. *Behav Res Ther* 2015; 73: 8-18.
 57. Parker G, Brotchie H. Gender differences in depression. *Int Rev Psychiatry* 2010; 22: 429-36.
 58. Hankin BL, Abramson LY. Development of gender differences in depression: description and possible explanations. *Ann Med* 1999; 31: 372-9.
 59. Nolen-Hoeksema S. Sex differences in depression. Stanford, CA: Stanford University Press, 1990.
 60. Marlowe N. Self-efficacy moderates the impact of stressful events on headache. *Headache* 1998; 38: 662-7.
 61. Lipchik GL, Smitherman TA, Penzien DB, Holroyd KA. Basic principles and techniques of cognitive-behavioral therapies for comorbid psychiatric symptoms among headache patients. *Headache* 2006; 46: S119-S132.
 62. Christiansen S, Jürgens TP, Klinger R. Outpatient combined group and individual cognitive-behavioral treatment for patients with migraine and tension-type headache in a routine clinical setting. *Headache* 2015; 55: 1072-91.
 63. Law EF, Beals-Erickson SE, Noel M, Claar R, Palermo TM. Pilot randomized controlled trial of internet-delivered cognitive-behavioral treatment for pediatric headache. *Headache* 2015; 55: 1410-25.
 64. Sharma P, Mehta M, Sagar R. Efficacy of transdiagnostic cognitive-behavioral group therapy for anxiety disorders and headache in adolescents. *J Anxiety Disord* 2017; 46: 78-84.
 65. Kang E-H, Park J-E, Chung C-S, Yu B-H. Effect of biofeedback-assisted autogenic training on headache activity and mood states in Korean female migraine patients. *J Korean Med Sci* 2009; 24: 936.
 66. Nestoriuc Y, Martin A, Rief W, Andrasik F. Biofeedback treatment for headache disorders: a comprehensive efficacy review. *Appl Psychophysiol Biofeedback* 2008; 33: 125-40.
 67. Rausa M, Palomba D, Cevoli S, et al. Biofeedback in the prophylactic treatment of medication overuse headache: a pilot randomized controlled trial. *J Headache Pain* 2016; 17: 87.
 68. Dindo L, Recober A, Marchman J, O'Hara MW, Turvey C. One-day behavioral intervention in depressed migraine patients: effects on headache. *Headache* 2014; 54: 528-38.
 69. Mo'tamedi H, Rezaemaram P, Tavallaie A. The effectiveness of a group-based acceptance and commitment additive therapy on rehabilitation of female outpatients with chronic headache: preliminary findings reducing 3 dimensions of headache impact. *Headache* 2012; 52: 1106-19.
 70. Day MA, Thorn BE, Rubin NJ. Mindfulness-based cognitive therapy for the treatment of headache pain: a mixed-methods analysis comparing treatment responders and treatment non-responders. *Complement Ther Med* 2014; 22: 278-85.
 71. Wells RE, Burch R, Paulsen RH, Wayne PM, Houle TT, Loder E. Meditation for migraines: a pilot randomized controlled trial. *Headache* 2014; 54: 1484-95.
 72. Tonelli ME, Wachholtz AB. Meditation-based treatment yielding immediate relief for meditation-naïve migraineurs. *Pain Manag Nurs* 2014; 15: 36-40.
 73. Calhoun AH, Ford S. Behavioral sleep modification may revert transformed migraine to episodic migraine. *Headache* 2007; 47: 1178-83.
 74. Smitherman TA, Walters AB, Davis RE, et al. Randomized controlled pilot trial of behavioral insomnia treatment for chronic migraine with comorbid insomnia. *Headache* 2016; 56: 276-91.
 75. Smitherman TA, Wells RE, Ford SG. Emerging behavioral treatments for migraine. *Curr Pain Headache Rep* 2015; 19: 13.
 76. Kropp P, Meyer B, Meyer W, Dresler T. An update on behavioral treatments in migraine - current knowledge and future options. *Expert Rev Neurother* 2017; 17: 1059-68.
 77. Altieri M, Di Giambattista R, Di Clemente L, et al. Combined pharmacological and short-term psychodynamic psychotherapy for probable medication overuse headache: a pilot study. *Cephalalgia* 2009; 29: 293-9.
 78. Andrasik F, Grazi L, Sansone E, D'Amico D, Raggi A, Grignani E. Non-pharmacological approaches for headaches in young age: an updated review. *Front Neurol* 2018; 9: 1009.
 79. Merikangas KR, Angst J, Isler H. Migraine and psychopathology. Results of the Zurich cohort study of young adults. *Arch Gen Psychiatry* 1990; 47: 849-53.
 80. Verri AP, Proietti Cecchini A, Galli C, Granella F, Sandrini G, Nappi G. Psychiatric comorbidity in chronic daily headache. *Cephalalgia* 1998; 18: 45-9.
 81. Mitsikostas D, Thomas A. Comorbidity of headache and depressive disorders. *Cephalalgia* 1999; 19: 211-7.
 82. Juang KD, Wang SJ, Fuh JL, Lu SR, Su TP. Comorbidity of depressive and anxiety disorders in chronic daily headache and its subtypes. *Headache* 2000; 40: 818-23.
 83. Zwart JA, Dyb G, Hagen K, et al. Depression and anxiety disorders associated with headache frequency. The Nord-Trøndelag Health Study. *Eur J Neurol* 2003; 10: 147-52.
 84. McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: results from a nationally representative sample. *Pain* 2004; 111: 77-83.
 85. Goulart AC, Santos IS, Brunoni AR, et al. Migraine headaches and mood/anxiety disorders in the ELSA Brazil. *Headache* 2014; 54: 1310-9.
 86. Fuller-Thomson E, Jayanthikumar J, Agbeyaka SK. Untangling the Association between migraine, pain, and anxiety: examining migraine and generalized anxiety disorders in a Canadian population based study. *Headache* 2017; 57: 375-90.
 87. Dindo LN, Recober A, Haddad R, Calarge CA. Comorbidity of migraine, major depressive disorder, and generalized anxiety disorder in adolescents and young adults. *Int J Behav Med* 2017; 24: 528-34.
 88. Lake AE, Saper JR, Hamel RL. Comprehensive inpatient treatment of refractory chronic daily headache. *Headache* 2009; 49: 555-62.
 89. Manlick CF, Black DW, Stumpf A, McCormick B, Allen J. Symptoms of migraine and its relationship to personality disorder in a non-patient sample. *J Psychosom Res* 2012; 73: 479-80.