1 Psychiatric Comorbidity in Migraine

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Introduction

The association of migraine with various psychological characteristics such as depressive tendencies, perfectionism and autonomic reactivity has been described by clinicians for more than a century. There is now abundant evidence from numerous large, population-based studies across a wide range of geographic sites that people with migraine have greater rates of mood and anxiety disorders. The data generated from such studies have also demonstrated the impact of comorbidity on the onset, course and severity of migraine, as well as use of services and response to treatment.

The goals of this chapter are to review: (i) the epidemiological evidence of psychiatric comorbidity in migraine; (ii) empirical evidence regarding the possible underlying mechanisms of these associations; (iii) the effects of psychiatric comorbidity on migraine course, severity and response to treatment; and (iv) the consideration of comorbidity in determining treatment for migraine patients. A case report illustrates the complex issues of psychiatric comorbidity.

Case report

Miss E. is 24 years old. She has been suffering from migraine without aura since adolescence. She consults now because her illness has become very incapacitating; for more than 6 months she has been experiencing one or more migraine attacks per week that persisted for two or three days. On those days, she takes one or two tablets of a combination anti-inflammatory and barbiturate, but she has begun taking these tablets more often during the past year. Therefore, medication overuse headache (MOH) is suspected. Her anxiety during the interview is impressive, and she confirms that she is currently 'stressed'. She is preparing for a competitive examination and has had difficulty concentrating on her work because of her headaches. She does not sleep well, ruminating during the night over what she could not do during the day. She suffers from guilt and accuses herself of having a 'lack of willpower'.

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Miss E. describes a history of anxiety since childhood. Her anxiety is generally focused on usual life stresses but she becomes far more anxious than she feels is warranted by the focal situation. Aside from anxiety, she has had excellent social and educational functioning. She reports brief, mild depressive episodes beginning at about age 16, with a first episode of depression occurring at the break-up of a relationship at age 18. She also reports periods of feeling better than usual during which she has more energy, is more active and sleeps two to three hours less per night. These periods last about four to five days and she returns to her usual pattern of sleep and activity afterwards. Her family history includes an alcoholic maternal grandfather and a mother's puerperal depression following birth of the patient's younger sister.

Miss E.'s headaches seem to have progressively worsened over the last three years. During this time, she has suffered from hypersomnia, abulia and anhedonia that persisted for about six months. Miss E. was treated with amitriptyline (75 mg/day) during the previous year but she became agitated and had a weight gain of about 12 kg over the past six months. Currently, she is being treated with atenolol (80 mg/day), but has not been taking the treatment for more than a month because it made her 'sleep too much'.

Overall, this young patient presents with migraine without aura, exacerbated by the onset of possible medication overuse headache during the past six months. The disorder worsened since she began to have depression, which was determined to be of moderate severity. On account of the family history of alcoholism and current medication overuse, there is a need for assessment of dependence on acute antimigraine drugs and other substances. The possible history of hypomanic episodes, anxiety disorders, and major depressive episodes, when considered together with her family history of maternal puerperal major depression and alcoholism in the paternal grandfather, raise concerns about bipolar mood disorder.

Association of migraine with affective disorders

Clinical and population studies of migraine have documented a two- to four-fold increase in mood disorders in people with migraine compared to those without migraine Table 1.1 [1–16]. Rates of comorbidity are far greater in clinical settings than in the general population. Studies of patients in tertiary care centres indicate that approximately 50% exhibit a significant increase in current depression scores [17,18]. Migraine may also predispose to more severe depression as the risk of suicide is greater in migraine than non-migraine patients even after controlling for the existence of depression [1,19]. The association between migraine and the bipolar subtype of depression has been reported to be greater than that for major depressive disorder alone; however, the lower prevalence of the bipolar subtype in many studies diminishes the power to discriminate differences across mood disorder subtypes [1,6,9,15,16,20–22]. Regardless, given the substantial comorbidity of migraine with mood disorders, it is imperative for clinicians to evaluate

migraine patients for the presence of depressive and manic symptoms in order to design a treatment regimen that can treat both disorders if necessary.

Migraine patients do not always spontaneously express their depressive complaints, which they readily ascribe to their headaches if they are frequent. As a matter of fact, depressive cognitions are often related to pain ('I am totally unreliable because of my migraine'; 'Things will never be better'…). If the patients are reluctant to accept the diagnostic of depression, the physician can rely on symptoms such as sleep disorders, lack of energy and loss of interest to have the patients accept the diagnostic.

Association of migraine with anxiety disorders

Anxiety disorders may have an even stronger association with migraine than mood disorders. There is a two- to six-fold increased risk for aggregate anxiety disorders as well as subtypes thereof among migraine sufferers compared with those without migraine Table 1.1. With respect to specific subtypes of anxiety disorders, panic attacks and disorder appear to have the strongest association with migraine, followed by phobic disorders and generalized anxiety disorder [1,2,5–7,9,11,12,15,16,23]. Perfectionism and obsessionality have been reported in clinical descriptions of people with migraine, but few studies have systematically evaluated this association. Although Breslau et al. [1] found that the prevalence of obsessive compulsive disorder was associated with migraine in the general population, this association has not been confirmed in several other studies [5,9]. The well-established co-occurrence of anxiety and depression has also been observed in population studies of people with migraine [10,24]. In general, the onset of anxiety in people with migraine is reported to occur in childhood and adolescence, but there is no evidence that anxiety occurs earlier among those with migraine in population surveys.

Anxiety in migraine patients mainly focuses on the fear of a new attack, which can induce the development of exaggerated avoiding behaviours towards trigger factors in phobic patients. Stress, by the way, is considered as a classical trigger factor for migraine attacks. Anticipating anxiety can also be a factor facilitating the development of medication overuse, when the patient takes medication at the slightest sign of a possible impending attack. Finally, some patients may develop panic attacks at the time of occurrence of migraine attacks if migraine headaches had previously been symptomatic of a serious event such as, for instance, a meningeal hemorrhage.

Association of migraine with substance dependence

The association between migraine and substance use disorders is somewhat contradictory. The increased odds of dependence on nicotine, alcohol and illicit drugs in subjects with migraine reported by Breslau et al. [1] was not replicated in most other studies [9,15,16] Table 1.1. Some of the

discrepant findings may be attributable to the lack of discrimination between licit and illicit drugs. People with migraine are at increased risk to develop abuse of drugs used to treat migraine such as painkillers and barbiturates. Around two-thirds of patients suffering from medication overuse headache are dependent on acute antimigraine drugs according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders IV) diagnostic criteria for behavioural loss of control of drug consumption and compulsive intake [25,26]. Migraine patients' susceptibility to addiction, and even that of their relatives, as suggested by the existence of dependence on licit substances (tobacco, anxiolytics, alcohol), might be a risk factor for the development of MOH [27]. The majority of studies show, however, that there is no association between alcohol use disorders and migraine.

Migraine and personality traits

Although the clinical literature provides numerous descriptions of the personality of patients with migraine, there has been limited empirical evidence for an association between migraine and either personality disorders or a specific constellation of personality traits [28]. Those studies that do purport to link personality traits to migraine suffer from several methodological shortcomings including: the lack of representative samples; absence of a control group; use of personality assessment instruments that were either not validated or validated only in psychiatric samples; and failure to consider the effects of age, gender, and coexisting anxiety and mood disorders.

The few population-based studies suggest that those with migraine exhibited significantly greater scores for neuroticism as compared with controls [28–32]. However, the neuroticism scores are not specific and may be more reflective of the presence of chronic pain. Results of smaller, clinical studies using the Minnesota Multiphasic Personality Inventory (MMPI) [32] confirm the data obtained in the general population: the 'neurotic triad' scores (hypochondria, depression, hysteria) are higher in headache patients, but still do not reach the pathological threshold.

Mechanisms of migraine comorbidity with psychiatric disorders

There are three basic mechanisms that could underlie psychiatric comorbidity with migraine:

1 Psychiatric disorders are a causal factor in the development of migraine.
2 Migraine is a causal factor in the development of psychiatric disorders (e.g., repeated and intense pain may lead to anticipating anxiety, perceived loss of control and other behavioral or cognitive risk factors for psychiatric syndromes).
3 A common shared etiological factor may explain the co-occurrence of both syndromes (e.g., a common genetic factor may result in abnormalities in neurotransmission, hormone regulation or other biological abnormalities) [33,34].

Table 1.1 Lifetime comorbidity of migraine and psychiatric disorders in population-based studies.

	Risk-ratio and confidence interval				
	Merikangas et al. 1990	Breslau et al. 1991	Swartz et al. 2000	Jette et al. 2008	Saunders et al. 2008
Comorbid disorder					
Major depressive disorder	2.2 (1.1–4.8)	4.3 (3.0–6.9)	3.2 (2.0–4.8)	2.3 (1.9–2.8)	3.5 (2.6–4.6)
Bipolar I and II	2.9 (1.1–8.6)	NS	7.3 (2.2–24.6)	3.7 (2.7–5.0)	3.9 (2.3–6.5)
Obsessive compulsive disorder	1.0 NS	5.1 (2.3–11.2)	NS	—	—
Generalized anxiety disorder	3.3	5.7 (2.7–12.1)	NS		2.5 (1.6–4.0)
Panic disorder	5.3			2.8 (2.2–3.6)	3.6 (2.4–5.2)
Social phobia	3.4 (1.1–10.9)	2.6 (1.5–3.3)	1.6 (1.3–2.2)	2.3 (1.9–2.9)	2.4 (1.8–2.3)
Nicotine dependence	—	2.2 (1.5–3.3)	—	—	4.6 (1.4–11.1)
Substance-related disorders	—	2.2 (1.5–3.3)	NS	1.0 (NS)	1.6 (0.9–2.9) NS
Any mental disorder	3.3 (0.8–13.8)	6.6 (3.2–13.9)	5.1 (2.6–9.8)	3.1 (2.4–4.1)	3.7 (2.2–6.2)

NS, non-significant.

Attempts to disentangle these three possible mechanisms have focused on assessing the order of onset of these conditions using longitudinal study designs, by measuring the change in severity of one disorder in the presence of comorbidity, and by examining the co-transmission of these disorders within families.

Few studies have assessed the order of onset of psychiatric disorders and migraine, and those available fail to provide a clear picture of the association amongst these conditions. Results from the Zurich Cohort Study show that anxiety disorders, including social phobia, simple phobia, agoraphobia, generalized anxiety disorder (GAD) and panic precede the onset of migraine headaches, which in turn precede the onset of affective disorders [5,35]. Similar results were obtained from the Dunedin Multidisciplinary Health and Development Study, which reported that individuals with migraine at age 26 had increased odds of an anxiety disorder at age 18 or 21 years [36]. Although results from the 13-year prospective follow-up of the Epidemiologic Catchment Area Study confirmed that a history of phobic disorder was predictive of the onset of migraine [9], they did not find that the onset of panic disorder systematically preceded that of migraine. In 1993, Breslau and Davis [2] found that migraine was also related to the subsequent onset of both major depression and panic disorder. Therefore, although the current evidence regarding order of onset suggests that migraine, anxiety and depressive disorders may co-occur because of common underlying etiologic factors, additional prospective research is necessary to obtain more conclusive evidence.

Findings of a linear relationship between headache frequency and the rate of comorbidity in the general population [11], and the association between the number of days with migraine and intensity of emotional distress [24] support the hypothesis of a common

underlying aetiology between emotional disorders and migraine. However, the specific risk factors have not yet been identified [5,37,38]. Possible mechanisms include alterations in monoamine systems or channelopathies [39], which have been considered in the pathogenesis of both migraine [20] and mood disorders [40]. Further research is needed to identify these potential pathways to migraine and mood/anxiety disorders.

Impact of psychiatric comorbidity on migraine

Several studies have investigated the clinical consequences of psychiatric comorbidity in individuals with migraine. The results of two French studies are shown in Figures 1.1–1.3. FRAMIG (Figures 1.1 and 1.2) was a nationwide, population-based postal survey, the objectives of which were to analyze the relationship between disability, quality of life and psychiatric comorbidity in migraine sufferers [24]. The objectives of the SMILE study (Figure 1.3) were to assess anxiety, stress, depression, functional impact and coping behaviors in 5417 consulting migraine patients [41]. Migraine patients with elevated anxiety and depression scores have worse quality of life than those patients without psychiatric comorbidity (Figure 1.1) [(10,16,21,24]. Similarly, psychiatric comorbidity in migraine patients is associated with increased disability

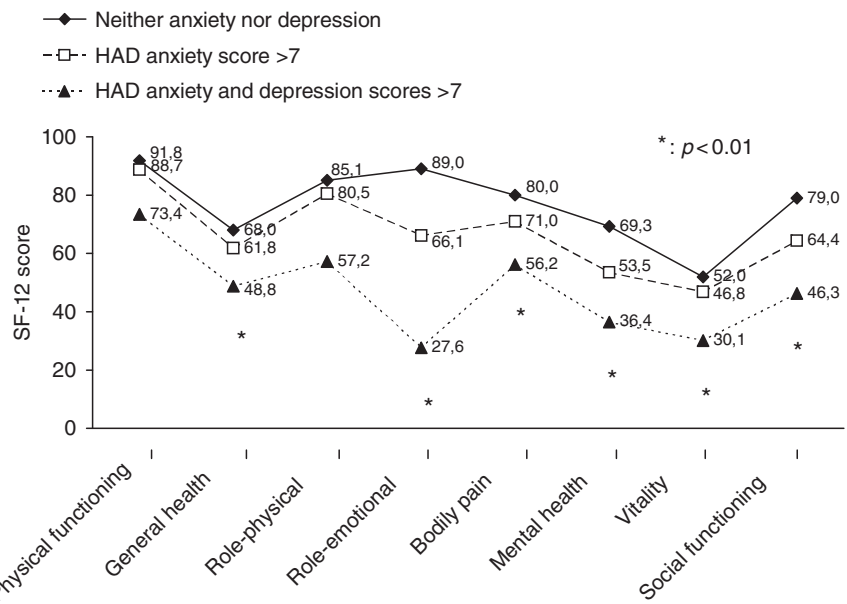

Figure 1.1 Influence of anxiety and depression (HAD scores) on health-related quality of life (SF-12) profile in FRAMIG study (population-based sample of migraine subjects). Migraine subjects with anxiety and those with both anxiety and depression differed significantly ($p < 0.01$) from migraine subjects with neither anxiety nor depression on all eight SF-12 dimensions except for physical functioning and role-physical.

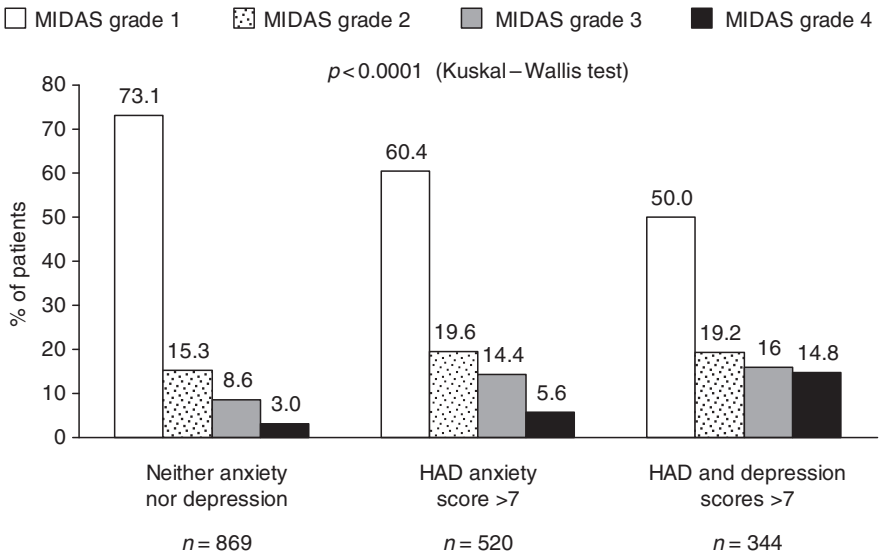

Figure 1.2 Influence of anxiety and depression (HAD scores) on migraine-related disability (MIDAS grade) in FRAMIG study (population-based subject sample).

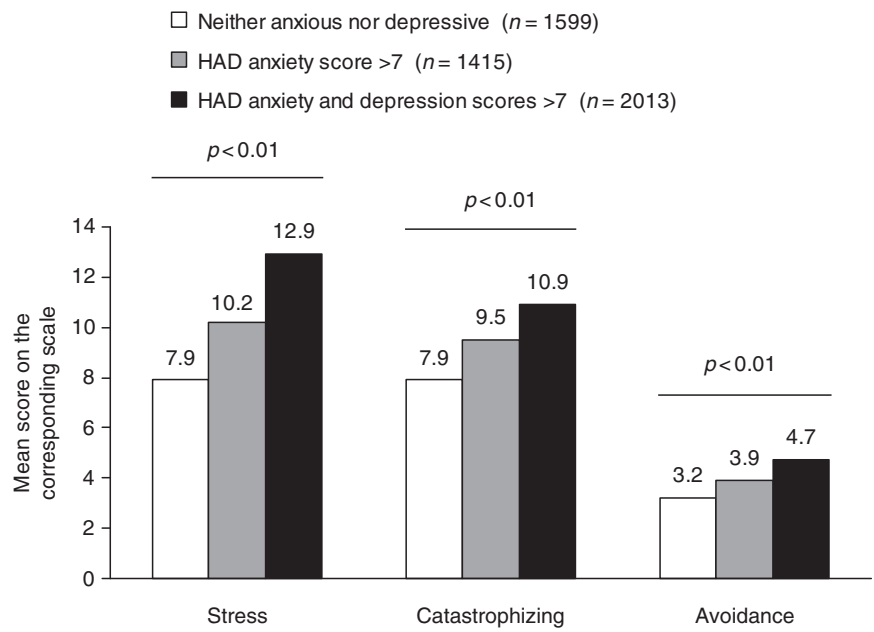

Figure 1.3 Effect of anxiety and depression (HAD scale) on perceived stress, catastrophizing and avoidance in SMILE study (sample of primary-care consulting migraine patients). Stress evaluated using the abridged form (PSS4) of the original Perceived Stress Scale questionnaire [59]; catastrophizing evaluated using the catastrophizing subscale of the Coping Strategies Questionnaire (CSQ) [60]; avoidance evaluated using the behavioral disengagement subscale of the brief version of the COPE inventory [61,62].

(as measured by the MIDAS score) (Figure 1.2) [24,41], and with an increase in direct costs related to migraine (such as those attributable to medications and health services) [42]. Moreover, a study by Radat et al. [41] indicates that perceived stress, catastrophizing and avoidance behaviors are more pronounced in migraine patients with elevated anxiety and depression scores than in migraine patients without psychiatric comorbidity (Figure 1.3). Finally, psychiatric comorbidity is associated with a greater number of days with migraine attacks, a greater number of days using acute antimigraine medications [41], and with poorer satisfaction with the efficacy of acute treatments [24]. This is in agreement with the finding that comorbidity with anxiety and depression is greater in patients with chronic migraine and up to four times greater in patients with MOH evolving from migraine than in those with episodic migraine [43,27]. Comorbidity with anxiety and depression, therefore, appears to be associated with both chronicity and analgesic abuse. These findings underscore the importance of identifying migraine patients suffering from psychiatric comorbidity as they are likely to display more severe symptoms, greater disability and report a worse quality of life [16].

Management

The strong association of migraine with both depression and anxiety should be considered in the treatment of individuals with migraine [44]. Systematic evaluation of the lifetime history of both depression and anxiety is necessary for determining optimal treatment strategies. Clinicians should systematically consider comorbid anxiety and mood disorders in selecting treatment options for people with migraine. Jette et al. [15] found that people from the general population with both a mental disorder and migraine were significantly more likely to take an antidepressant than those with either depression or anxiety alone or migraine alone. In general, comorbid depression and anxiety are more relevant for the selection of a migraine prophylaxis than for that of an acute antimigraine treatment. The use of prophylactic medications with side effects of lassitude, fatigue or depression should be avoided, if possible. If not, careful clinical evaluation of the above-cited manifestations of depression, including anergia, hypersomnia and irritability, should be monitored. Additionally, in patients with medication overuse headache evolving from episodic migraine, it is critical to evaluate the potential for dependence on acute antimigraine drugs, which would impose specific management of the behavior underlying drug consumption.

Regarding pharmacological options for treatment, the major classes of drugs that have been investigated in the prophylaxis of migraine include the β-adrenergic blocking agents, antidepressants, anticonvulsants, calcium channel blockers and aspirin [44]. The beta-blockers have been the most widely prescribed class of drugs for migraine prophylaxis; however, clinicians should be particularly cautious in prescribing this class of drugs to individuals with a history of depression, since the

beta-blockers are associated with the development of anhedonia, irritability and lassitude, which may occur after many months on any of these agents. In contrast, patients with high levels of autonomic anxiety may actually benefit from this class of drugs.

The tricyclic antidepressants have been well-established as prophylactic agents for migraine; however, the side effects of amitriptyline include sedation and weight gain. Secondary amines (e.g., nortriptyline and desipramine) appear to be efficacious in the treatment of depression, and have fewer side effects than do the parent tertiary amines (e.g., amitriptyline, imipramine). Conversely, the selective serotonin reuptake inhibitors (SSRIs) have not demonstrated efficacy in migraine. In fact, some patients complain of headache as a secondary effect of the latter class of drugs [45]. Introducing the SSRI very slowly reduces this inconvenience. The combination of these drugs with triptans poses a theoretical risk of inducing serotoninergic syndromes. In practice, the risk appears extremely low and related to the addition of a third serotoninergic drug or the use of elevated doses [46]. In the future, dual serotonin and norepinephrine (noradrenaline) reuptake inhibitors may be established as effective drugs for the preventive treatment of migraine in patients with anxious and depressive disorders [47–49].

The monoamine oxidase inhibitors (MAOIs), which have been demonstrated to be superior to other classes of antidepressants in the management of depression with atypical features [50], have also been reported to be efficacious in the treatment of migraine headache [51,52]. However, this class of drugs should be reserved for people with frequent and severe migraine accompanied by atypical depression and anxiety disorders.

Antiepileptic drugs such as valproate and, to a lesser extent, topiramate, may be useful for mood regulation in patients with bipolar mood disorders or, for divalproate specifically, the treatment of bipolar depression [53]. Worthy of note is that depression can be an adverse effect of topiramate. Nevertheless, bipolarity should be carefully assessed in depressed patients and these drugs preferentially given to bipolar subjects over antidepressants since antidepressants can precipitate a mood switch.

There has been substantial research on the use of behavioral treatments including biofeedback, relaxation training, and cognitive-behavioral therapy for migraine prevention. Alternative treatments of relaxation (and/or biofeedback) and cognitive-behavioral therapy have demonstrated their efficacy in the prophylactic treatment of migraine [54–56] but overall their efficacy is below that of pharmacological treatments. They can, however, be effectively associated with the latter, in particular in stress-sensitive subjects. The efficacy of interpersonal and cognitive therapy for the treatment of acute episodes of depression may also extend to the treatment of depression in the context of migraine. These approaches may be particularly useful for migraine patients with anxious anticipation of attacks, which can lead to MOH, as well as those patients for whom stress is a predominant trigger factor of attacks [57]. Stress perception and dysfunctional coping strategies such as catastrophizing and avoidance can be targeted by psychotherapeutic interventions [58].

Case report: treatment approach

In a first step, ambulatory withdrawal was proposed to Miss E. after two consultations with center physicians (a neurologist and a psychiatrist) and an interview with the nurse. These interviews were intended to assess the current medical condition, to make treatment objectives clear for the patient and to initiate therapeutic education. In particular, we educated the patient in the keeping of a headache diary, with a record of intakes of acute antimigraine treatments. During the withdrawal period, the patient was asked to take no more than two tablets per week of frovatriptan (the acute treatment was changed) and we initiated a preventive treatment with valproate. The selection of this drug was based on the possibility that the patient's mood disorder pertained to the bipolar spectrum. Withdrawal headaches staggered over the first five days and were bravely endured by the patient. To help her, we proposed psychological support and relaxation sessions. Relaxation therapy was proposed on the basis of one session per week during the first two months, and we advised the patient to complement them with a stress management therapy. Evolution was favorable, both concerning migraine as well as mood.

Conclusion

There is substantial evidence for the association of migraine with psychiatric disorders. This review of the literature suggests the following:

1 Individuals with migraine show increased odds of developing depressive disorders or anxiety disorders, especially panic attacks, generalized anxiety and phobic disorders, as well as bipolar mood disorders.
2 The mechanisms of comorbidity likely comprise both common risk factors and causal links. Repercussions of comorbidity include alterations in onset, course and severity of migraine; greater deterioration of quality of life; and increase in the frequency of intake of antimigraine drugs, which increases the probability that episodic migraine will evolve to MOH. The management proposed to the patient will then take this aspect into account.
3 Potential treatments for migraine accompanied by depression include antidepressants and other mood regulators; they may simultaneously lead to remission of symptoms of migraine and co-occurring depression, anxiety and bipolar mood disorders.

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