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The Associations Between Migraine, Unipolar Psychiatric Comorbidities, and Stress-related Disorders and the Role of Estrogen

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Abstract

Migraine is a common and often disabling neurovascular disorder. It has been linked with several psychiatric disorders, such as depression and anxiety, and to stress-related disorders, such as abuse and posttraumatic stress disorder (PTSD). Epidemiological data have consistently shown a higher prevalence of migraine, depression, anxiety, abuse, and PTSD in women as compared with men. The increased vulnerability of women to migraine and psychiatric disorders often occurs during periods of marked hormonal fluctuations of ovarian hormones. One consequence of these associations is the hypothesis that estrogens have a role in the pathophysiology of both disorders. This article offers an in-depth review of several studies linking psychiatric disorders and stress-related disorders with migraine. We also discuss the role of estrogen in the pathophysiologic overlap between these disorders. Finally, we briefly touch on where future research may be headed, in light of these data.

Introduction

Migraine is a common and often disabling neurovascular disorder [1]. It has been linked with various medical conditions such as hypertension, obesity, and stroke [2,3], as well as with several psychiatric disorders such as depression and anxiety [4]. More recently, stress-related disorders, such as those caused by abuse and posttraumatic stress disorder (PTSD), have been shown to be associated with migraine [5–7,8•].

The disease burden of migraine may be magnified when psychiatric comorbidities are present. In addition, their presence may cloud the differential diagnosis, lead to poor adherence to treatment regimens, and prolong and complicate the course of disease [9]. Identifying and delineating the presence and interaction of psychiatric comorbidities in migraine patients may help guide treatment, steering the physician away from certain modalities and toward others. For example, β-blockers would be less desirable in a migraineur with depression, whereas in migraineurs with PTSD, cognitive-behavioral therapy should be considered [4,8•].

There are several possibilities for the occurrence of psychiatric comorbidities with migraine. One theory is that psychiatric factors are a rare cause of headaches. Conversely, it could be that the mental burden of continuous or severe migraines can cause or contribute to various psychiatric dysfunctions. The third and most unifying theory is that these disorders share

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common pathophysiological abnormalities that can give rise to both conditions, such as genetic factors or abnormalities in serotonergic processing and responses to estrogen [4,10].

This article reviews several of the studies linking psychiatric disorders and stress-related disorders with migraine. We then discuss areas of pathophysiologic overlap between these disorders, with a focus on the influence of estrogen. Finally, we briefly touch on where future research may be headed, in light of these data.

Depression and Migraine

Migraine and depression are highly prevalent disorders. In addition, epidemiologic studies consistently report higher rates of both disorders in women. While migraine prevalence (either definitive or probable) has been estimated to occur in 34.5% of women and 20.1% men, depression has been estimated to occur in 12.6% of women and 6.3% of men in the United States [1,11]. Furthermore, numerous studies in the United States and other countries have demonstrated a higher occurrence of both disorders with each other than could occur just by chance alone [12–30]. The following section evaluates the studies establishing that depression and migraine are comorbid disorders.

The prevalence of depression is greater in definitive and probable migraineurs than in nonmigraineurs

The first general population study to demonstrate an association between migraine and depression was conducted by Merikangas et al. [13]. A total of 457 young Swiss adults between 27 and 28 years old were assessed for migraine and various psychiatric conditions. The diagnosis of migraine was modeled based on the guidelines from the Ad Hoc Committee for the Classification of Headache. The diagnosis of psychiatric disorders was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III criteria. Although neither brief recurrent depression nor dysthymia had a significant association with migraine, migraineurs did have an increased odds of major depression (OR, 2.2; 95% CI, 1.1, 4.8). This finding was further supported by data from the Midlife Development in the United States Survey (MIDUS), which evaluated the associations between several pain and psychiatric disorders, including depression and migraine. It also extended the findings to a larger age range [15]. More than 3000 US adults between 25 and 74 years old were evaluated. Migraine in the past year was self-reported by participants, and depression was assessed using several measures from the Composite International Diagnostic Interview-Short Form (CIDI-SF). Almost 29% of subjects with migraine were reported to be depressed compared with 12% of subjects without migraine (OR, 2.84; 95% CI, 2.19, 3.70).

Two Canadian general population studies also found an association between migraine and depression. Molgat and Patten [18] used a large-scale probability sample survey of the Canadian population to compare the strength of the depression and migraine association. Major depressive episodes were evaluated using the CIDI-SF for major depression, and the presence of migraine was determined by self-report of a clinician diagnosis of migraine within the preceding year. More than 130,000 participants were used for the sampling procedures. Of those with migraine, 17.6% (95% CI, 16.6, 18.6) fulfilled criteria for depression, whereas only 7.8% (95% CI, 7.5, 8.0) of those with other chronic conditions and 7.4% (95% CI, 7.2, 7.6) of controls fulfilled depression criteria. In the second Canadian general population study, Jette et al. [19] also identified migraineurs by self-report of a health care professional diagnosis of migraine, and depression was determined by the World Mental Health Composite International Diagnostic Interview (WMH-CIDI). Of all migraineurs, 8.6% (95% CI, 7.3, 9.8) fulfilled criteria for major depressive disorder compared with 3.4% (95% CI, 3.1, 3.7) of those without migraine. The lifetime prevalence of depression was also greater in migraineurs (18.8%) compared with nonmigraineurs

(9.8%). Finally, a battery of health-related outcomes (eg, disability, level of activities, quality of life, overall mental health) were found to be worse in those with migraine and depression compared with those who suffered with either of the conditions alone.

The relationship between depression and migraineurs has also been shown to extend to those migraineurs missing one criteria to fulfill definitive migraine (ie, probable migraineurs). Patel et al. [20] evaluated 8579 members of a Health Alliance Plan, utilizing the International Classification of Headache Disorders (ICHD) criteria for the diagnoses of definitive and probable migraine. Depression was determined by the Primary Care Evaluation of Mental Disorder (PRIME-MD) for depression. Those patients with definitive migraine had a higher prevalence of depression (OR, 2.57; 95% CI, 2.08, 3.18), than controls. Those with probable migraine also had a higher prevalence of depression (OR, 1.90; 95% CI, 1.53, 2.36).

The association of depression with migraine is stronger in migraineurs with aura compared with those without aura

A Norwegian general population study by Oedegaard et al. [21] evaluated the migraine–depression association, and evaluated the differences in this association when migraine was subdivided as migraine with aura and without aura. More than 49,000 participants were included. Depression was assessed using the Hospital Anxiety and Depression Scale, and migraine was evaluated using modified ICHD criteria. Migraineurs of both genders had an increased prevalence of depression compared with those without migraine. In addition, women migraineurs with aura had a stronger likelihood to have depression (OR, 2.24; 95% CI, 1.57, 3.18) than those women with migraine without aura (OR, 1.30; 95% CI, 1.06, 1.61). However, in men there was no significant difference in the presence of depression in those with migraine with aura compared with those without aura.

The modification of the migraine–depression association when subdivided as migraine with or without aura is further supported by a recent study by Samaan et al. [22] and extends to include male migraineurs with aura. More than 1250 adult participants with recurrent depression were evaluated for probable migraine, as well as for migraine with and without aura and compared with 851 controls who were screened for an absence or low liability to anxiety or depression. The psychiatric history was ascertained using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN). Migraine classification was based on the ICHD-II criteria. Participants with recurrent depression had a significantly greater chance of having nonmigrainous headache (OR, 2.56; 95% CI, 2.04, 3.2). Furthermore, this association grew even stronger for those with either probable migraine (OR, 3.64; 95% CI, 2.7, 5) or migraine without aura (OR, 3.67; 95% CI, 2.2, 6.14), and was greatest in those with migraine with aura (OR, 5.63; 95% CI, 3.54, 9.00).

The odds of major depression are greater in women with CDH compared with those with episodic headache

The relationships between depression, chronic headaches, and somatic symptoms were evaluated by Tietjen et al. [16] in a multicenter study of 1032 women. Information detailing their headache subtypes, headache severity, somatic symptoms, and presence of depression was obtained from all participants. Headache criteria were based on the ICHD-II; headache-related disability was determined utilizing the Headache Impact Test (HIT)-6; depression was evaluated using the Patient Health Questionnaire (PHQ)-9; and somatic symptom severity was determined based on the PHQ-15. Chronic daily headache (CDH) sufferers were three times more likely to report more severe somatic symptoms (OR, 3.4; 95% CI, 1.6, 7.3) and four times more likely to report major depression (OR, 4.4; 95% CI, 2.9, 6.5) than their episodic counterparts. In addition, the risk of major depressive disorder increased

dramatically in the subset of women with frequent, disabling migraines and severe somatic symptoms (OR, 31.8; 95% CI, 12.9, 78.5).

The prevalence of depression remains increased even in older migraineurs

Migraine may be comorbid with depression in older individuals as well as in younger adults. Camarda et al. [23] evaluated the association of migraine and psychiatric disorders in Italian adults over the age of 50 years, using the ICHD criteria for the diagnosis of migraine and the Center for Epidemiologic Studies Depression Scale (CES-D) for depression. A total of 1436 participants fulfilled depression criteria, and 151 fulfilled migraine criteria. More than 47% of those with migraine exhibited mild to moderate depressive symptoms compared with only 16% of controls ($P < 0.0001$). After adjusting for demographics, the relationship persisted with mild to moderate depressive symptoms being strongly associated with migraines for women (OR, 4.7; 95% CI, 3.1, 7.0) and men (OR, 6.2; 95% CI, 2.8, 14.6). These findings further support the findings of Molgat and Patten [18], in which the data were stratified by age; and in which for migraineurs older than 58, the depression prevalence was 10.2% (95% CI, 16.6, 18.6) compared with only 3.8% (95% CI, 3.5, 4.2) for older adults with other chronic conditions and 3.8% (95% CI, 3.5, 4.1) for nonmigraine controls.

Depression and migraine are comorbid disorders

Breslau et al. [12,14,24] have conducted three longitudinal studies examining the migraine–depression relationship—each with similar results. Most recently, this association was evaluated in a longitudinal general population survey of adults 25 to 55 years of age, suffering either from migraine or depression or both [14]. A computer-assisted telephone interview (CATI) was used to assess for migraine utilizing the ICHD-I criteria, and depression was evaluated using the World Health Organization Composite International Diagnostic Interview (WHO-CIDI). In this study, depression predicted first migraine (OR, 3.4; 95% CI, 1.4, 8.7). Furthermore, the initial diagnosis of migraine predicted depression during the duration at the study (OR, 5.8; 95% CI, 2.7, 12.3). Although not true for nonmigraine headaches, this study established a bidirectional relationship between depression and migraine or the comorbidity of depression and migraine.

Anxiety and Migraine

As with depression, anxiety is a common unipolar mood disorder that has been linked to migraine. It has been estimated that the lifetime prevalence rate of anxiety in the United States is 28.8%, and the 12-month prevalence is 18.1% [25,26]. Like migraine, anxiety disorders have a female predilection, occurring in twice as many women as men [27]. Several studies (reviewed below) have also demonstrated that migraine and anxiety are associated.

Migraineurs have an increased odds of generalized anxiety disorders

In the general Swiss population survey of 27 and 28 year olds, Merikangas et al. [13] also identified an association between migraine and anxiety and between migraine and social phobias. In migraineurs, the odds of generalized anxiety disorders (GADs) were increased fivefold (OR, 5.3; 95% CI, 1.8, 15.8) and that for social phobias by threefold (OR, 3.4; 95% CI, 1.1, 10.9). Furthermore, after controlling for general anxiety, major depression no longer emerged as a significant predictor of migraine on its own. Its effect was suggested to be likely due to the strong association of depression with general anxiety.

Breslau and Davis [28] also evaluated the association between migraine and anxiety. In a longitudinal general population study of 1007 young adults, (between 21 and 30 years of age), participants were evaluated for migraine using the ICHD criteria, and for psychiatric

disorders utilizing DSM-III criteria. GAD was more prevalent in migraineurs (OR, 5.7; 95% CI, 2.7, 12.1). In addition, the odds ratio of obsessive compulsive disorder was increased in migraineurs (OR, 5.1; 95% CI, 2.3, 11.2), as well as the odds for panic disorders (OR, 6.6; 95% CI, 3.2, 13.9). Moreover, a history of migraine significantly increased the rate of first-time panic disorder (OR, 12.8; 95% CI, 4.1, 39.8).

McWilliams et al. [15] likewise evaluated the relationship between GAD, panic attacks, and migraines. Migraine was self-reported, and psychiatric disorders were determined utilizing the DSM-IIIR. Of the 3032 participants, 9.1% of those with GAD also self-reported migraine in the past year compared with 2.5% of those without GAD (OR, 3.86; 95% CI, 2.48, 6.00). In addition, 17.4% of migraineurs fulfilled criteria for panic disorder compared with only 5.5% of nonmigraineurs (OR, 3.58; 95% CI, 2.59, 4.97).

Recently, a similar relationship between anxiety and migraine was demonstrated in a Malaysian case-control study, in which 70 subjects who fulfilled ICHD-II criteria for migraine and 70 age-, gender- and race-matched controls were evaluated [30]. The Minnesota Multiphasic Personality Inventory-2 (MMPI-2) questionnaire was used to assess for anxiety and anxiety traits. Slightly more than 34% of migraineurs exhibited anxiety traits compared with 16% of controls (OR, 2.80; 95% CI, 1.16, 6.83; $P = 0.011$). In addition, women migraineurs were noted to be more anxious than men migraineurs.

The odds of GAD in migraineurs increase with increasing headache frequency

A Norwegian general population study of 43,478 participants also supports the relationship between migraine and anxiety. Furthermore, this study identified a correlation with anxiety based on headache frequency [29]. Whereas migraine was identified using modified ICHD-II criteria, anxiety was assessed using the Hospital Anxiety and Depression Scale (HADS). Migraineurs were found to have a higher likelihood of having a coexisting anxiety disorder, even after adjusting for depression (OR, 2.7; 95% CI, 2.4, 3.1). In addition, the frequency of migraine headaches correlated with the existence of anxiety disorders, with a twofold increased risk of GAD in those with migraines occurring less than 7 days per month (OR, 2.3; 95% CI, 2.0, 2.7), a sixfold increased risk in those with 7 to 14 days of migraine per month (OR, 5.6; 95% CI, 4.6, 6.8), and a sevenfold increased risk for GAD in those with migraines occurring more than 14 days a month (OR, 6.9; 95% CI, 5.1, 9.4).

The association of anxiety and depression with migraine is stronger in women migraineurs with aura compared with those without aura

A comparison of anxiety disorder in patients with migraine with and without aura was undertaken by Oedegaard et al. [21]. Those who suffered from anxiety (both genders separately and all participants combined) were more likely to have migraine with or without aura compared with controls. When subdivided as those with aura and compared with those without aura, there was no statistical difference in the comorbidity of anxiety alone with either migraine subtype (OR, 1.0; 95% CI, 0.8, 1.2). However, anxiety and depression together were more likely in women with migraine with aura than in those without aura (OR 1.6; 95% CI, 1.2, 2.1) [21].

Migraineurs with anxiety and depression have greater disability and a poor quality of life than those without either disorder

The impact of depression and anxiety on migraineurs was explored by Lanteri-Minet et al. [17]. A total of 1179 adult migraineurs from the FRAMIG 3 survey (the first nationwide population-based survey carried out in France using the ICHD-II criteria for migraine) were evaluated. Migraine was determined based on the ICHD-II criteria, and depression and anxiety were determined by the French version of HADS. Disability was evaluated using the

MIDAS and Short Form Health Survey (SF-12) questionnaires. The proportion of participants with anxiety or anxiety and depression was significantly higher among migraineurs compared with controls ($P < 0.01$). In addition, subjects with depression alone or anxiety alone had significantly lower or poorer health-related quality-of-life scores on most of the SF-12 scales than those without either disorder ($P < 0.01$). Furthermore, migraineurs with both anxiety and depression had significantly lower SF-12 scores than migraineurs with anxiety alone ($P < 0.01$). Finally, although those with migraine and depression alone or migraine and anxiety alone were statistically the same across all grades of headache-related disability (MIDAS), migraineurs with both depression and anxiety were more likely to fall into more severe MIDAS grades.

Migraineurs with anxiety or depression have a poorer response to treatment and incur higher health-related costs

The response to treatment in migraineurs with anxiety and other comorbid psychiatric disorders has been shown to be poorer than those migraineurs without psychiatric comorbidities [17]. Specifically, in one study, participants with both migraine and depression reported less pain relief 2 hours after acute migraine therapy, decreased treatment tolerability, less rapid resumption of activity, and decreased satisfaction with the treatment compared with migraine sufferers without anxiety or depression.

Migraineurs with anxiety or depression also incur greater costs in consuming health care. In a study that collected health data for clinical utilization (including outpatient prescription drugs and other health-related expenditures) from more than 100 payers of 11,332 adults, migraineurs who suffered from anxiety or depression alone or anxiety and depression combined had higher inpatient, outpatient, and prescription drug costs compared with controls [31]. In addition, outpatient, prescription drug, and total medical cost per year was greater in migraineurs with both anxiety and depression ($13,442) than those with just anxiety ($10,223) and those with just depression ($10,223). In contrast, migraineurs without either of these comorbidities had total medical costs of $5590. Thus, this study suggests that the presence of unipolar psychiatric disorders such as anxiety or depression in migraineurs is not just associated with a greater disease burden but also a greater individual and societal financial burden.

Abuse, Posttraumatic Stress Disorder, and Migraine

In recent years, PTSD has become an increasingly recognized disorder, with a lifetime prevalence of 8% in the general population [8•]. In addition, the lifetime prevalence of PTSD is twice as common in women as in men. Despite the clinical perception that military combat is the most common etiology, the most common causes of PTSD are interpersonal traumas, such as from physical and sexual abuse [32]. In the United States, it has been estimated that 22% of women report physical abuse and 17% report sexual abuse. These numbers are significantly higher in those with migraine or psychiatric disorders [5].

Childhood abuse is associated with an increased risk of migraine

A history of childhood abuse is associated with migraine. In one general population study evaluating self-reported migraine and abuse in more than 3000 respondents 25 to 74 years of age, childhood abuse was found to be significantly related to an increased odds of migraine (OR, 2.7; 95% CI, 1.2, 5.8) [33]. This finding is supported by a recent clinic-based study of more than 900 female migraineurs by Tietjen et al. [34•], in which women with migraine and depression had a greater frequency of childhood abuse than those migraineurs without depression ($P < 0.001$).

Physical and sexual abuse may be associated with an increased risk of migraine chronification

An abuse history in migraineurs may also be associated with migraine chronification. In a clinic-based study of 161 adult migraine patients, Peterlin et al. [5] evaluated the frequency of abuse reported by both episodic migraineurs and those with CDH. Headache diagnoses were based on ICHD-II criteria, and histories of physical and/or sexual abuse were self-reported. Physical and/or sexual abuse was reported by more CDH sufferers (40%) than those with episodic migraine (27.3%) ($P < 0.05$).

Migraineurs with concomitant psychiatric disorders report more abuse than those without psychiatric disorders

The presence of psychiatric comorbidities in conjunction with migraine may also be an indicator of a possible abuse history. Specifically, in a clinic-based study of 223 adult female migraineurs, Tietjen et al. [6] found that physical and sexual abuse was reported more commonly in migraineurs with anxiety and depression compared with those without anxiety and depression. In addition, migraineurs with psychiatric comorbidities were more likely to have higher current psychosocial stress scores ($P < 0.001$).

PTSD is reported in more migraineurs (14%–23%) than noted in the general population (6%–8%). Furthermore, PTSD may be a risk factor for migraine chronification in those migraineurs with depression [8•,35]. In the first study to suggest an association between headache and PTSD, de Leeuw et al. [36] evaluated 80 headache patients (with either migraine or tension-type headache). Of the headache participants, 26% fulfilled PTSD criteria on the PTSD Check List-Civilian (PCL-C), a finding that is notably higher than the 8% PTSD prevalence reported for the general population. This finding was later confirmed in both a general population study [35] and a large, clinic-based population study of migraineurs [8•].

In a general population study of more than 5000 participants, Saunders et al. [35] showed that 14.1% of migraineurs fulfilled PTSD criteria compared with 2.6% of those without any headaches. Similarly, Peterlin et al. [8•] evaluated PTSD in episodic migraineurs and furthermore evaluated the frequency in those with CDH. Specifically, a total of 30.3% of CDH sufferers and 22.4% of episodic migraineurs fulfilled PTSD criteria. In addition, headache-related disability (HIT-6) was noted to be greater in both episodic migraineurs and CDH sufferers with PTSD compared with those without PTSD ($P = 0.002$).

PTSD may also be associated with migraine chronification and abuse [8•]. Specifically of those headache sufferers with depression, the PTSD frequency was greater in CDH sufferers (24.6%) than in episodic migraineurs (15.8%), whereas in those migraineurs without depression and PTSD, there was no difference in the frequency of CDH sufferers (6.5%) compared with episodic migraine participants (5.2%). Finally, the frequency of physical and sexual abuse and its association with PTSD in headache sufferers was evaluated. While 43.1% of CDH sufferers and 41.7% of those with episodic migraine reported physical and/or sexual abuse, when the presence of abuse was evaluated in those headache sufferers with PTSD, 72.9% of CDH sufferers and 60% of episodic migraineurs reported physical and/or sexual abuse [8•].

When these studies that evaluated abuse and PTSD in migraineurs are taken together, they suggest that abuse and PTSD should at least be screened for in migraineurs. In addition, cognitive-behavioral therapy should be considered in those migraineurs with an abuse history or PTSD.

The Role of Estrogen

Several lines of evidence (eg, epidemiological, clinical, basic science studies) support the hypothesis that the comorbidity of mood disorders (eg, depression, anxiety) and migraine is linked to estrogen. First, the prevalence of migraine and mood disorders occurs more commonly in women than men [1,11]. Second, women's increased vulnerability to migraine and mood disorders occurs during periods of marked hormonal fluctuations. A female predisposition is first shown during puberty, with evidence of stabilization during pregnancy, followed by exacerbations 1 week after childbirth, and finally perimenopausal increases that persist to approximately 51 to 55 years of age [37,38]. One consequence of these associations is the hypothesis that estrogens have a role in the pathophysiology of both disorders.

Specifically, estrogen withdrawal has been suggested to play a role in both disorders. In 1959, Dalton [39] showed that nearly half of women admitted to psychiatric hospitals for various symptoms were admitted immediately before or during menstruation. Similarly, in 1972, Somerville [40] suggested that estrogen withdrawal was associated with migraine. In addition, women are uniquely at risk for estrogen withdrawal disorders such as premenstrual dysphoric disorder, postpartum depression, menstrually related migraine, and postpartum exacerbation of migraine [41,42]. Although a review of the literature linking migraine to estrogen is beyond the scope of this article, the following section reviews some of the data linking estrogen to mood and stress-related disorders, and where it may overlap with migraine pathophysiology.

The use of estrogen to treat mood disorders spans over a century, with a case report of 36 women with various neuropsychological conditions being treated with ovarian extracts, which was published in 1900 [43]. Despite the interest, many questions still remain about the use of estrogen in mood disorders. Many of the human studies evaluating the efficacy of estrogen in depression have limitations, including lack of uniformity of the regimen of hormone therapy, variations in the exposure-dependent effects of estrogen, and lack of uniformity in participant enrollment. However, when taken together, the data are suggestive that estrogen monotherapy and estrogen augmentation of some therapies may be of benefit to women with depression (Table 1) [44–50]. Specifically, estrogen augmentation of tricyclic antidepressants and selective serotonin reuptake inhibitors has limited data suggesting possibly efficacy for depression in women (Table 1) [51–54]. Given that both tricyclic antidepressants and fluoxetine have data supporting their efficacy in migraine prevention, and given the comorbidity of depression and migraine, future research may evaluate the effectiveness of antidepressants in conjunction with estrogen therapy in migraineurs [55,56].

How estrogen may be linked to mood and stress-related disorders and migraine is complex [57–62]. For obvious reasons the role of estrogen in medical disorders has focused on women, but it is important to note that estrogens and estrogen receptors are present in both men and women [57–60]. And in both genders, estrogens have multiple important physiological roles, including organizational effects on developing neurons, activational effects on mature neurons, and modulation of synapse formation. Furthermore, estrogens have been shown to modulate neurotropic factors and neuropeptides implicated in both migraine and mood disorders, including neuropeptide Y, corticotrophin-releasing hormone, and the neurotransmitters (serotonin, dopamine, and glutamate) [37,57].

Mood disorders and migraine may be linked through commonalities in pathways associated with estrogen and its receptors. Estrogen and its receptors have been shown to be highly localized in the hypothalamus. Activation or modulation of the limbic system and

hypothalamic-pituitary-adrenal (HPA) axis has been linked to the pathophysiology of both mood disorders and migraine in humans [37,57]. Furthermore, animal studies have shown that proestrous (high-estrogen) females exhibit greater HPA axis responses to an acute stressor relative to males and diestrous (low-estrogen) females. Physiologically relevant doses of estradiol alone or in combination with progesterone attenuate stress-induced activation of frontal cortex, hippocampal, and hypothalamic neurons in response to acute stressors. The decrease in central stress responsivity following estrogen treatment may account for the antidepressant and anxiolytic effects of estrogen and possibly also play a role in pain modulation [59].

The biological effects of estrogens are mediated by binding to estrogen receptor (ER)-α and ER-β. In addition to their presence in the hypothalamus, both receptors have also been demonstrated in the adipose tissue of women and men [63]. Whereas ER-α exhibits no difference in distribution based on depot location or gender, the ER-β receptor is present in lower quantities in visceral adipose tissue compared with subcutaneous adipose tissue (by fivefold in women and threefold in men) [61,62]. In addition, obesity has been shown to be associated with an increased prevalence of both depression and stress-related disorders (eg, from abuse), as well as an increased prevalence of migraine [8•,63–68]. The effect of obesity on the prevalence of migraine has been shown to vary based on gender and the distribution of adipose tissue [3]. Furthermore, obese migraineurs with depression alone, with anxiety alone, or depression and anxiety together have been shown to have higher headache frequencies and greater headache-related disability compared with non-obese migraineurs [68]. Thus, the effects of estrogen on both mood disorders and migraine may be mediated centrally through interactions with ERs of the hypothalamus and peripherally through adipose tissue.

Finally, serotonin (5-HT) has been implicated in the pathophysiology of mood disorders and migraine, and estrogen modulates serotonin. Specifically, the ER-β mRNA has been shown to be present in the dorsal raphe nuclei where the major serotonergic cell bodies reside [69]. In addition, estrogen has been shown to promote the synthesis of 5-HT through the induction of tryptophan hydroxylase, the rate-limiting enzyme in the synthesis of 5-HT, as well as to reduce 5-HT reuptake transporter mRNA expression in the dorsal raphe nuclei. Estrogen also upregulates 5-HT1 receptors and downregulates 5-HT2 receptors [10]. Overall, estrogen exhibits an agonistic effect on the serotonergic system and thus may be an important link as to how the pathophysiology of migraine and mood disorders overlap.

Conclusions

As with migraine, unipolar mood disorders (eg, depression, anxiety) and stress-related disorders (eg, PTSD) are disproportionately prevalent in women. Extensive epidemiological data also support that migraine and mood disorders are comorbid. Although associated with multiple methodological limitations (and limited to no clinical research in men), several lines of evidence suggest a role for estrogen and its receptors in mood disorders and migraine. How estrogen affects mood disorders and migraine is complex, but at least in part has been linked to modulation of the HPA axis and 5-HT. In order to truly advance our knowledge as to the role of estrogen in mood disorders and migraine, future basic and clinical research evaluating these disorders needs to take into account the effect of estrogen in both genders, as well as the life-cycle stage and hormonal cycle of women.

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Table 1

Estrogen as monotherapy for depression

Study	Population (menopausal status)	Diagnosis method	Patients, *n*	Duration	Treatment	Study design	Results
Campbell and Whitehead [47]	POST (age not reported)	Depression: BDI	68	2 mo per drug	CEE (6.25 mg/d) vs placebo	PC, DB, XO	ET > P
Klaiber et al. [46]	PRE (mean age, 32); POST (mean age, 49)	Resistant MDD: DSM-II	50	3 mo	CEE (15–25 mg/d) vs placebo	PC, DB	ET > P; significant drop in HAM-D scores in CEE-treated group
Coope [48]	PRE and PERI (ages 40–60)	Mild to moderate depression: BDI	55	6 mo per drug	Estrone sulphate (1.5 mg/d) vs placebo	PC, DB, XO	ET = P
Schmidt et al. [49]	PERI (age not reported)	MDD: DSM-III	20	6 wk	CEE (0.625 mg/d) vs placebo	PC, DB	ET > P
Schmidt et al. [45]	PERI (ages 44–55)	Minor or MDD: DSM-III	34	3 or 6 wk	Transdermal 17β-estradiol (50 μg/d) vs placebo	PC, DB	ET > P; partial or full remission in 80% with E_2 vs 20% with placebo
Soares et al. [44]	PERI (ages 44–55)	MDD or minor dysthymic disorder: DSM-IV	50	3 mo	Transdermal 17β-estradiol (100 μg/d) vs placebo	PC, DB	ET > P; remission in 68% with E_2 vs 20% with placebo
Cohen et al. [50]	PERI and POST (ages 42–57)	MDD: DSM-IV	22	1 mo	Transdermal 17β-estradiol (100 μg/d) vs placebo	Open label	ET > P; remission in 67% of women (remission = MADRS < 10)
Shapira et al. [51]	PRE and POST (ages 26–74)	MDD: DSM-II	11	1 mo	Imipramine (200 mg) + CEE (1.25–3.75 mg) vs imipramine (200 mg) + placebo	PC, DB, XO	Imipramine + ET = imipramine + placebo
Schneider et al. [52]	POST (mean age, 67.9)	MDD: DSM-III	367	6 wk	ET + fluoxetine vs ET + placebo vs fluoxetine alone vs placebo alone	Retroanalysis of PC, DB	Fluoxetine + ET > fluoxetine + placebo
Amsterdam et al. [53]	Women > 45 years on HT or no HT; women and men < 45 years	MDD: DSM-IIIR	568 (40 women > 45 on HT)	12 wk	HT + fluoxetine vs fluoxetine alone	Open label	Fluoxetine + HT = fluoxetine alone
Schneider et al. [54]	POST (age > 60)	MDD: DSM-IIIR	127	12 wk	ET + sertraline (*n* = 34) vs sertraline alone (*n* = 93)	Retroanalysis of PC, DB	Sertraline + ET > sertraline alone on CGI (HAM-D results not significant)

BDI—Beck Depression Inventory; CEE—conjugated equine estrogen; CGI—Clinical Global Impressions; DB—double blind; DSM—Diagnostic and Statistical Manual of Mental Disorders; ET—estrogen therapy; HAM-D—Hamilton Scale of Depression; HT—hormone therapy (estrogen and progestin); MADRS—Montgomery-Asberg Depression Rating Scale; MDD—major depressive disorder; P—placebo; PC—placebo controlled; PERI—perimenopausal; POST—postmenopausal; PRE—premenopausal; XO—crossover.