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Post-Traumatic Stress Disorder and Migraine: Epidemiology, Sex Differences, and Potential Mechanisms

B. Lee Peterlin, DO, **Satnam S. Nijjar, MD**, and **Gretchen E. Tietjen, MD**
From the Department of Neurology, Johns Hopkins University, Bayview Medical Center, Baltimore, MD, USA (B.L. Peterlin and S.S. Nijjar); Department of Neurology, University of Toledo, Toledo, OH, USA (G.E. Tietjen)

Abstract

Migraine is a common, often disabling disorder associated with a significant personal and societal burden. The presence of post-traumatic stress disorder (PTSD) may increase this disability substantially. Migraine and PTSD are both up to 3 times more common in women than in men. The divergence in prevalence rates of migraine and PTSD that occurs between the sexes after puberty suggests that gonadal hormones play an important role. In addition, the preponderance of PTSD in women may be related to their higher rates of interpersonal trauma, the most common cause of PTSD. However, recent data suggest that although the odds of PTSD are increased in both women and men with episodic migraine, this association is stronger in men than women. In this paper, we examine the epidemiology of PTSD and migraine, with an emphasis on the known sex differences. We then discuss the neurobiological changes associated with PTSD, the current hypotheses for the mechanisms relating PTSD and migraine, and the treatment implications of these findings.

Keywords

headache; migraine; post-traumatic stress disorder; anxiety; physical abuse; sexual abuse; maltreatment; sex; women; men

Migraine and post-traumatic stress disorder (PTSD) are both up to 3 times more common in women than in men.[1] The divergence in prevalence rates of migraine and PTSD that occurs between the sexes after puberty suggests that gonadal hormones play an important role. In addition, the preponderance of female PTSD sufferers has been suggested to be due to the higher rates of interpersonal traumas (eg, physical and sexual abuse) which occur in women as compared to men. Interpersonal trauma is the most common cause of PTSD.[2,3] However, recent data suggest that although the odds of a lifetime or 1-year period prevalence rate of PTSD are increased in both women and men with episodic migraine, this association is stronger in men than women.[4,5] In this paper, we examine the epidemiology suggesting an association between PTSD and migraine,[3–8] with an emphasis on known sex differences.[4] This is followed by a discussion on the neurobiological changes associated with PTSD and the current hypotheses of how PTSD and migraine may be associated. We close with a discussion of the treatment implications.

Address all correspondence to B.L. Peterlin, Neurology, Johns Hopkins University, Bayview Medical Center, 4940 Eastern Avenue, Baltimore, MD. lpeterlin@jhmi.edu.

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POST-TRAUMATIC STRESS DISORDER: DEFINITION AND EPIDEMIOLOGY

Exposure to traumatic life stressors is associated with an increased risk of several psychiatric disorders, including generalized anxiety disorder (GAD), depression, and PTSD.[9] Although PTSD is an anxiety disorder, it is distinctly separate from (although often associated with) other anxiety disorders such as panic and GAD.[10] PTSD occurs as a result of trauma arousing feelings of intense fear, helplessness, and horror in the exposed individual. The individual's response characteristically involves emotionally re-experiencing the event, numbing of affect, and avoidance of stimuli which are associated with the event, as well as increased arousal.[7,11] See Table 1 for the full Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IVR) criteria for PTSD.[12]

The lifetime prevalence rate of PTSD is approximately 5–8%.[5,13] Averaged over the lifespan, PTSD is twice as common in women as men. However, in those between 21 and 25 years of age, the female to male ratio is nearly 3 to 1.[13,14] Although life-threatening traumas (eg, military combat) are associated with an 8.5-fold increase in PTSD risk compared with other types of trauma,[15] the most common causes of PTSD are interpersonal traumas. Interpersonal traumas, such as physical and sexual abuse, occur more commonly in women than men.[2] Further, PTSD prevalence rates have been estimated at between 26% and 52% among women who have experienced childhood abuse and related interpersonal violence.[16] Other risk factors for the development of PTSD include: low socio-economic status, lack of social support, minority status, history of psychiatric illness, and early separation from parents.[17]

POST-TRAUMATIC STRESS DISORDER AND MIGRAINE EPIDEMIOLOGY

A growing body of epidemiological literature supports an association between migraine and PTSD.[3–8] PTSD prevalence rates have been demonstrated to be increased in those with migraine in multiple different cohorts, including tertiary pain and headache clinics, veteran cohorts, and general population surveys.[3–8] In the tertiary, clinic-based studies, approximately 22–30% of headache sufferers fulfilled PTSD criteria.[3,6] In a veteran cohort survey, the prevalence of PTSD was even greater than found in the tertiary care clinics, with almost 50% of those with migraine fulfilling criteria for PTSD.[8] Finally, in a general population survey of over 5600 participants, the 12-month and lifetime odds ratio of PTSD in episodic migraineurs was noted to be greater than the odds ratio for either major depression or generalized anxiety in episodic migraineurs (Fig. 1). Episodic migraineurs had a 3- to 4-fold greater odds of PTSD than those without headache (life: OR 3.07, CI: 2.12–4.46; 12-month: OR 4.34, CI: 2.73–6.89).[4,5] Additionally, the 12-month PTSD prevalence rates were 14.3% in episodic migraineurs and lifetime PTSD prevalence rates were 21.5% in episodic migraineurs as compared to those without headache (2.1% 12-month and 4.5% lifetime).[4]

In order to fulfill criteria for PTSD, at least 1 traumatic life event must be noted (Table 1).[12] A general population study, using data from the National Comorbidity Survey Replication, reported that irrespective of PTSD status, episodic migraineurs have more traumatic stressors (4.6 ± 3.6) than those without headache (2.6 ± 2.5).[4] In addition, the most common traumatic life events reported in a clinical study of 80 headache patients included learning about a family member or close friend who was hurt or killed, sudden injury or auto accident, observing someone being hurt or killed, and violent attacks.[6] These findings were supported by a second tertiary clinic-based study of almost 600 migraineurs, with similar traumatic events being reported as witnessed, learned about, or happening directly to the participants, including natural disaster, sudden violent death, combat and transportation accidents.[3] However, in this study, of the total participants who fulfilled PTSD criteria and

reported a traumatic life event as having “happened to me,” the most commonly reported traumas included transportation accidents, sudden unexpected death of a loved one, and physical and sexual assault. Furthermore, in this same study, 60% of episodic migraineurs with PTSD reported physical or sexual abuse as a traumatic life event. It is also notable that 42% of all episodic migraineurs, irrespective of PTSD presence, reported physical or sexual assault.[3]

Sex differences in the PTSD–migraine association have been specifically evaluated in only one study to date.[4] In a general population study of 5692 participants, the sex-specific odds ratio of PTSD in episodic migraineurs were compared to those without headache. Although the odds ratio of PTSD were increased in both women and men with migraine as compared to those without headache, the odds were significantly greater in men with migraine as compared to women with migraine. Specifically, male migraineurs had a 3- to 4-fold greater odds ratio of PTSD than female migraineurs (Table 2, Fig. 2).[4]

POTENTIAL MECHANISMS FOR THE ASSOCIATION BETWEEN PTSD AND MIGRAINE

The neurobiological mechanism by which PTSD is associated with migraine is not known. However, of those with episodic migraine and PTSD, 69% reported symptoms related to PTSD before the onset of severe or frequent headache.[4] And although causality cannot be determined from this cross-sectional study, it suggests that the presence of PTSD may be associated with an increased predisposition to the development of migraine. Additionally, sex hormones may at least modify the association, given the greater odds of PTSD in male migraineurs than female migraineurs.

Hypotheses for the possible mechanisms contributing to the PTSD–migraine association include dysfunction of the autonomic system and the hypothalamic-pituitary-adrenal (HPA) axis. Supportive of the presence of sympathetic dysfunction, serotonin and norepinephrine levels have been demonstrated to be lower in both those with PTSD and those with migraine.[18–21] In addition, peripheral adrenergic hypersensitivity and clinical symptomatology related to sympathetic nervous system dysfunction (eg, orthostatic symptoms and pupillary differences) have been described in migraineurs.[22] Similarly, lower heart rate variability in women with PTSD and in patients with combat-related PTSD[23–25] has been described, and is consistent with excessive cardiac sympathetic modulation, inadequate parasympathetic modulation, or both.[26]

The majority of studies examining baseline HPA axis function in PTSD suggest high levels of cortisol in those with exposure to traumatic events but low levels in those who have already developed PTSD.[27,28] The low level of cortisol in those with PTSD may reflect a compensatory response to elevated levels occurring shortly after a traumatic event, with higher levels being predictive of later PTSD development.[27,28] Several studies have suggested that migraineurs may have baseline elevated cortisol levels.[29–31] In addition, one study has shown a decreased serum cortisol response following low-grade cognitive stress in migraineurs,[32] while another has shown an increased cortisol response following administration of human corticotrophin-releasing hormone.[33] These data suggest that migraineurs may have a greater biological risk for developing PTSD when exposed to traumatic events and an abnormal response to HPA activation with stressors.

Abnormalities in the immune response to the HPA axis may also contribute to the association between PTSD and migraine. It is known that the HPA axis exhibits a bidirectional relationship with the immune system, and when the HPA axis is functioning normally, cortisol increases are associated with a suppression of cytokines.[34] PTSD has been

shown to be associated with both lower levels of cortisol and elevations of several proinflammatory cytokines (which have also been implicated in migraine) including tumor necrosis factor (TNF)-alpha, interleukin (IL)-1β, and IL-6.[34,35] Thus, it is possible that having PTSD which is associated with low cortisol levels, results in an increase in proinflammatory cytokines and contributes to migraine development or maintenance.

POTENTIAL MECHANISMS FOR THE SEX DIFFERENCES IN THE PTSD–MIGRAINE ASSOCIATION

It is unclear why the PTSD–migraine association is stronger in men than women. However, similar findings have been noted in a capsaicin-induced pain study, in which 10 men and 10 women received topical capsaicin for 30 minutes on the face and on the ankle in a second session. Although women rated the pain higher than men, men reported more anxiety related to the pain.[36]

The age of the occurrence of the traumatic life event resulting in PTSD may be an important factor for the sex differences in the PTSD–migraine association. When a traumatic life event occurs before the age of 13 years, the risk of major depression is greater than the risk of PTSD; however, when the traumatic life event occurs after 12 years of age, the risk of PTSD is greater.[37] Although the migraine population has a documented high prevalence of abuse, the peak age of vulnerability for childhood sexual abuse is under 13 years of age.[38–40] In contrast, transportation accidents and combat (two of the most common traumatic events reported by migraineurs with PTSD) may be more commonly experienced by those older than 12 years of age.[3] It is therefore plausible that in the migraine population, sex differences in the type and age of traumatization contribute to the sex differences in the risk of PTSD.

There are several potential mechanisms for the sex differences in the association between PTSD/anxiety and migraine/pain including structural changes of subcortical brain regions as a result of PTSD, as well as genetic influences, and sex differences in the HPA axis response. In children with PTSD from abuse, alterations in structure of the frontal cortex and cerebellum as well as smaller corpus callosum volumes have been reported; notably, the corpus callosum alterations were more prominent in boys than girls.[41–43] In adults with early abuse-related PTSD, imaging studies have demonstrated reduced volumes of the hippocampi and the right anterior cingulate cortex.[44,45]

Genetics may also play a role in the sexual dimorphism in the PTSD–migraine association. Specifically, there are a number of recent studies analyzing various single nucleotide polymorphisms of genes implicated in human anxiety disorders, including PTSD.[46–48] In one such study, men homozygous for the variant brain-derived neurotrophic factor (BDNF met) gene were noted to exhibit significantly increased anxiety-related traits compared to noncarriers.[46] BDNF has also been implicated as a mediator of trigeminal nociceptive plasticity, which is important in central sensitization, a key mechanism of migraine pathophysiology.[49]

Sex differences in the response of the HPA axis to stress may also contribute to the sex differences seen in the PTSD–migraine association. First (although conflicting data exist), a general trend suggests a greater acute HPA response in adult men as compared to women, with a greater HPA response in men to achievement- or performance-related stressors and possibly a greater response in women with social rejection tasks.[50] Second, a functional magnetic resonance imaging study has demonstrated increases in cerebral blood flow (CBF) in the right prefrontal cortex and CBF reduction in the left orbitofrontal cortex to psychological stress in men. In contrast, women primarily activated the limbic system,

including the anterior cingulate cortex and insula. Furthermore, the prefrontal activity in men was associated with increases in salivary cortisol, whereas the limbic activation in women showed a lower degree of correlation. It is of note that all of these previously mentioned brain areas which were activated in the men and women of this study are also regions which have been shown to play a role in the affective processing of pain.[50]

It has also been suggested that the HPA axis response in men, which has been shown to be associated with a greater cortisol-releasing hormone (CRH)-stimulated adrenocorticotropic hormone (ACTH) and exercise-stimulated cortisol response than women, may leave men more vulnerable to some stressors.[51] Alternatively, it has also been suggested that the female stress response may be more "buffered" than men's because of a greater production of estrogen and oxytocin, both which may help counter the effect of cortisol.[50–52] Further research with attention to the sex differences in migraineurs with PTSD is warranted.

TREATMENT IMPLICATIONS

Several studies have shown that PTSD has a negative impact on the disability of chronic pain patients.[53,54] In addition, data suggest that migraine sufferers with PTSD have significantly greater disability than those without PTSD.[3] Specifically, in 1 multi-center study, the headacheimpact test (HIT)-6 in episodic migraine participants with PTSD (65.2 ± 6.1) was greater than those without PTSD (61.7 ± 6.8) even after adjusting for demographics and depression (P = .0018).[3]

No studies to date have evaluated the effect of PTSD therapy on migraine severity, disability, or frequency in those migraineurs with PTSD. However, data suggest that behavioral PTSD treatment alone can positively influence chronic pain conditions and disability.[54,55] The use of cognitive/behavioral therapy (alone or in combination with pharmacological therapy) should therefore be considered in migraineurs with PTSD.

CONCLUSIONS

Migraine and PTSD are more prevalent in women than men. Although both women and men migraineurs have greater odds of PTSD than those without migraine, male migraineurs may have even greater odds of suffering from PTSD than female migraineurs.[4] The mechanism for this association is not known. However, dysregulation of the autonomic system and HPA axis as well as structural alterations in the corpus callosum in response to PTSD may play a role.[20,29,31–33,43]

The presence of PTSD in migraineurs is associated with greater headache-related disability than in migraineurs without PTSD;[3,4] and data suggest that behavioral PTSD treatment alone can positively influence chronic pain conditions and disability.[54,55] Taken together, the current data suggest that migraineurs, and in particular male migraineurs, should be screened for PTSD and that cognitive/behavioral therapy (alone or in combination with pharmacological therapy) should be considered.

Further research on the association between PTSD and migraine, with attention to sex differences, as well as to treatment implications, is warranted.

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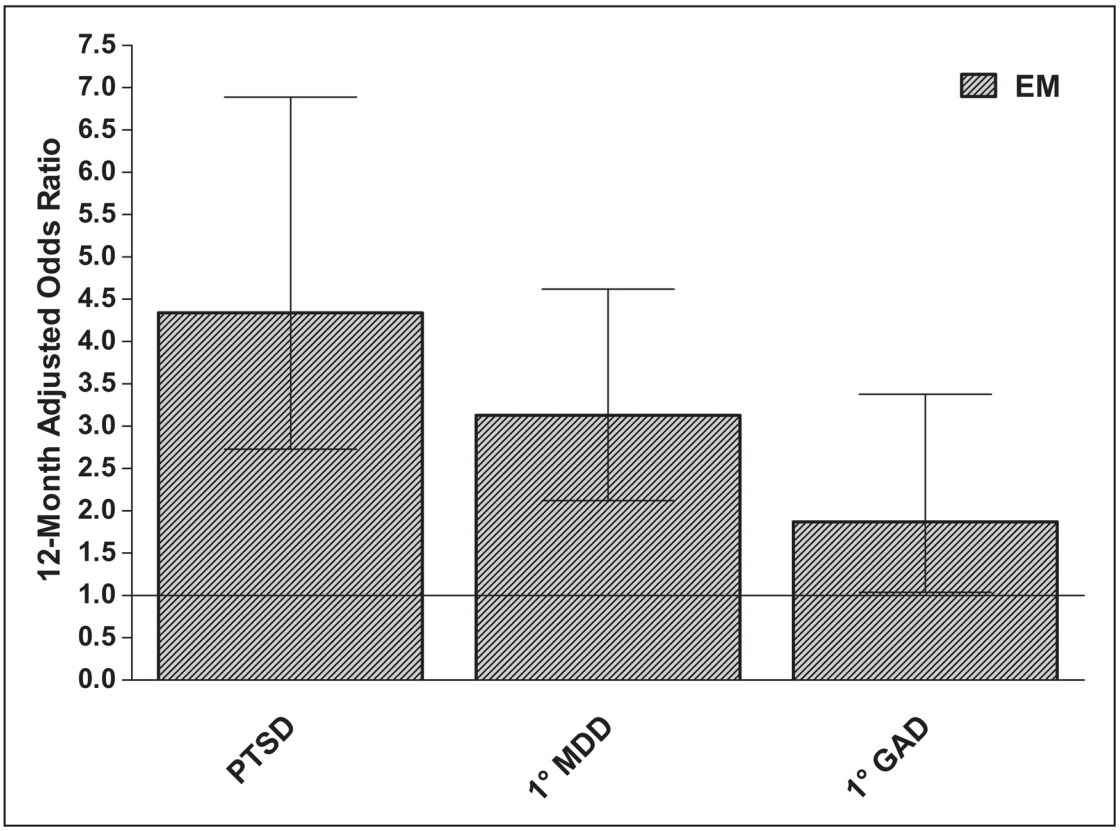

Fig 1.

Adjusted odds ratios of mood disorders in migraine. EM, episodic migraine; PTSD, post-traumatic stress disorder; MDD, major depressive disorder; GAD, generalized anxiety disorder. Figure created based on data from reference (3).

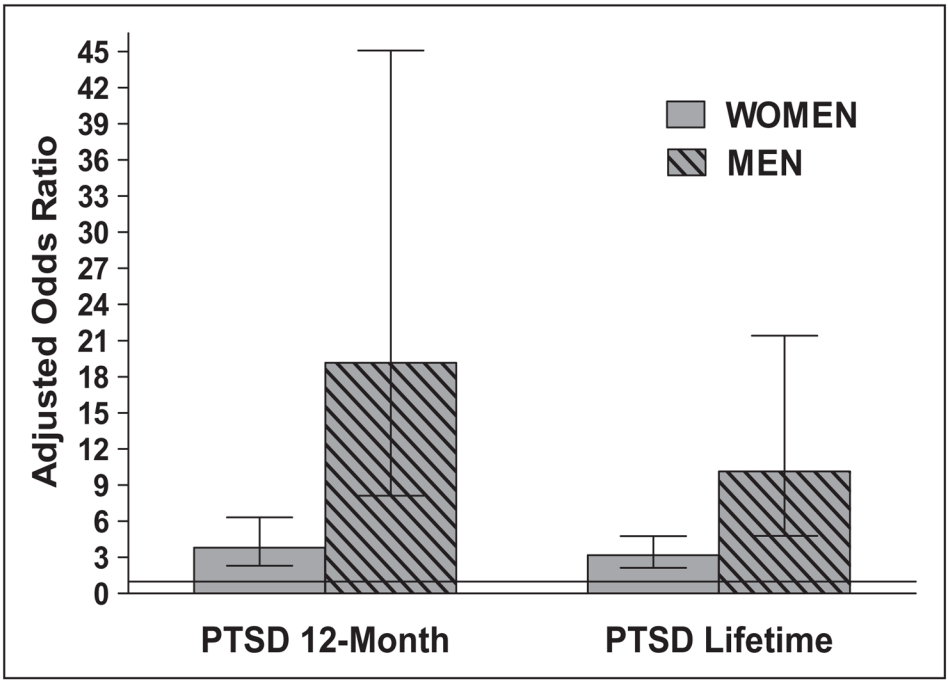

Fig 2.
Sex-specific odds ratio of post-traumatic stress disorder (PTSD) in episodic migraine. Figure created from data from reference (3).

Table 1

Diagnostic and Statistical Manual, Fourth Edition, Text Revision Criteria for Post-Traumatic Stress Disorder

Criterion A: exposure to traumatic stressor
Exposure to a traumatic event in which both of the following have been present:

1. The individual has experienced, witnessed, or been confronted with an event or events that involve(s) actual or threatened death, serious injury, or a threat to the physical integrity of oneself or others.
2. The individual's response involved intense fear, helplessness, or horror.

Criterion B: intrusive recollection
The traumatic event is persistently re-experienced in at least *one* of the following ways:

1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions.
2. Recurrent distressing dreams of the event.
3. Acting or feeling as if the traumatic event were recurring (includes sensation of reliving the experience, illusions, hallucinations, and dissociative flashback episodes).
4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
5. Physiologic reactivity upon exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

Criterion C: avoidance/numbing of responsiveness
Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by at least *three* of the following:

1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
3. Inability to recall an important aspect of the trauma
4. Markedly diminished interest or participation in significant activities
5. Feeling of detachment or estrangement from others
6. Restricted range of affect (such as not being able to have loving feelings)
7. Sense of foreshortened future (such as not expecting to have a career, marriage, or a normal lifespan)

Criterion D: hyper-arousal
Persistent symptoms of increasing arousal (not present before the trauma), indicated by at least *two* of the following:

1. Difficulty falling or staying asleep
2. Irritability or outbursts of anger
3. Difficulty concentrating
4. Hyper-vigilance
5. Exaggerated startle response

Criterion E: duration
Duration of the symptoms in B, C, and D is greater than 1 month.

Criterion F: functional significance
The disturbance causes clinically significant impairment/distress in the individual's social, occupational, or other important areas of functioning.

Table 2

Sex-Specific Prevalences, Odds Ratios, and 95% Confidence Intervals for the Association Between Episodic Migraine and Post-Traumatic Stress Disorder

	Women				Men			
	No HA n (%)	**Episodic Migraine n (%)**	**Model 1 OR (CI)**	**Model 2 OR (CI)**	**No HA n (%)**	**Episodic Migraine n (%)**	**Model 1 OR (CI)**	**Model 2 OR (CI)**
PTSD Lifetime	141 (6.6)	42 (20.8)**	3.19 (2.14, 4.76)	2.77 (1.83, 4.21)	58 (2.6)	12 (24.5)**	10.14 (4.80, 21.40)	6.86 (3.11, 15.11)
PTSD 12 months	67 (3.1)	26 (12.9)**	3.82 (2.31, 6.32)	3.44 (2.03, 5.82)	27 (1.2)	10 (20.4)**	19.15 (8.13, 45.07)	19.70 (8.08, 48.05)

** $P < .001$ as compared to those with no headache; Model 1 = OR (95% CI) adjusted for age, marital status, race, education, and smoking; Model 2 = OR (95% CI) adjusted for age, marital status, race, education and smoking and other DSM primary lifetime.

In addition to demographics, model 2 lifetime odds ratio are adjusted for other lifetime odds ratio of primary MDD, GAD, ETOH abuse and lifetime odds ratio of any drug abuse, while 12-month odds ratio are adjusted for 12-month odds ratio of primary MDD, GAD, ETOH abuse and 12-month odds ratio of any drug abuse.

Table modified from data from reference (3).

CI = confidence interval; DSM = Diagnostic and Statistical Manual; ETOH = alcohol; GAD = generalized anxiety disorder; HA = headache; MDD = major depressive disorder; OR = odds ratio; PTSD = post-traumatic stress disorder.