

# INTRODUCTION AND EPIDEMIOLOGY OF PSYCHIATRIC COMORBIDITIES FOR MIGRAINE

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Doctor: “Of course you have headaches all the time—you’re depressed! If you get help for your depression and get less stressed, you’ll be fine.”

Patient: “Of course I’m depressed! I have these horrible headaches. Fix them and I’ll be fine.”

There has been extensive epidemiological research showing an association between migraine and psychiatric disorders. The psychiatric comorbidities of migraine include depression, bipolar disorder, anxiety, Post-traumatic Stress Disorder (PTSD), stress, history of abuse, and sleep disorders.<sup>1-4</sup> (Table 1) These comorbid psychiatric conditions can increase the risk of migraine-related disability and quality of life, migraine chronification, and poor treatment outcomes.<sup>5</sup> There are some hypotheses for the association between migraine and psychiatric comorbidities. At this time, there is limited research on how to best treat migraineurs with psychiatric comorbidities.

## **Depression**

Depression is one of the most common psychiatric comorbidities in migraine patients. A UK study showed that 47% of migraine patients had depression compared to only 17% of non-migraine patients.<sup>6</sup> A Detroit study using telephone/household interviews had similar findings - 40.7% of migraine patients had depression compared to 16% without of non-migraine patients.<sup>7</sup> A third study by Zwart et al. using the Hospital Anxiety and Depression Scale (HADS) found that migraine patients were 2.7 times more likely to have depression than non-migraine patients.<sup>8</sup> The association is even stronger in patients with chronic migraine.<sup>9</sup> While at this time there is no evidence that improved control of depression helps with remission, it is important to identify depression in migraine patients because it is a significant predictor of migraine chronification.<sup>9</sup> Identification of depression in migraine patients may also affect choice of treatment; some anti-depressants have also been shown to be effective in treating migraines.<sup>10</sup> However, the efficacy of some tricyclic anti-depressants to treat migraines suggests a shared mechanism.<sup>11</sup>

## **Anxiety Disorders**

Anxiety disorders are two to five times higher in migraine patients compared to the general population and two times more common in migraine patients than depression.<sup>12</sup> In fact, significant depressive symptoms rarely occur alone in migraine patients. Depression is almost always comorbid with anxiety. The majority, 51-58%, of migraine patients will meet criteria for at least one anxiety disorder in their lifetime. Effective management of anxiety associated with migraine can help patients increase their overall quality of life and allow migraine treatments more of an opportunity to work. As with depressive disorders, anxiety is more prevalent in patients with chronic migraine as opposed to non-chronic patients. Anxiety is problematic because migraine patients with anxiety disorders spend \$4634 more per year in healthcare dollars than those migraine patients without anxiety, and \$7500 more than persons without migraine or psychiatric conditions.<sup>13</sup> Anxiety has also been shown to be more disabling than depression in migraineurs.<sup>14</sup>

Depression
Anxiety
Bipolar Disorder
Stress
Posttraumatic Stress Disorder (PTSD)
Abuse
Substance Abuse
Sleep Disorders

### ***Bipolar Spectrum Disorder***

Migraine is also associated with bipolar spectrum disorder. Migraine patients are three times more likely to have Bipolar Disorder, particularly migraine patients with aura.<sup>15-17</sup> Conversely, migraine is found in about 25% of bipolar disorder patients<sup>18</sup>. Interestingly, bipolar disorder and migraine share similar characteristics. They are both episodic, worsened by stress, respond to anti-epileptic medication, and have a positive family history of affective disorders and migraine.<sup>19</sup> One study suggested that migraine in depressed patients may be a bipolar spectrum trait.<sup>20</sup>

### ***Stress***

Stressful life events and major life events are associated with stress and migraine. Chronic migraine patients have been found to have more major life events in the year before the chronification of their migraines compared to episodic migraine patients.<sup>21</sup> Major life events shown to be associated include change of residence, employment status, marital status, changes related to their children, deaths of relatives or close friends, and “extremely stressful” ongoing situations. An analysis of data from the ELSA-Brasil demonstrated that the occurrence of negative life events, particularly financial hardship and hospitalization, had a direct and independent association with migraine.<sup>22</sup>

Within the body, chronic stress affects both peripheral and central nociception, causing allodynia, hyperalgesia, and chronic head pain. Anxiety and stress may affect migraine patients’ allostatic load, comprised of conditions affecting the brain’s ability to maintain physiologic stability. This may result in impaired glucose tolerance at the time of the headache, dysfunction in the autonomic nervous system, decreased heart rate variability, changes in baroreflex sensitivity, increased levels of pro-inflammatory cytokines, and hormonal changes such as nocturnal peaks in prolactin, delayed nocturnal peaks in melatonin, increased amounts of cortisol, and changes in the menstrual cycle.<sup>23</sup> Interestingly, medication overuse can also affect allostasis. Rainero et al. showed that chronic migraine patients with medication overuse headache have their corticotrophic and somatotrophic systems dysregulated compared to normal controls.<sup>24</sup> Stress management in migraine patients can reduce the onset of a migraine and prevent a migraine-stress cycle in which the stress from having a migraine can trigger another migraine.<sup>25</sup>

### ***Post-Traumatic Stress Disorder (PTSD)***

In comparison to the 1-12% prevalence of post-traumatic stress disorder (PTSD) in the general population, the prevalence of PTSD among migraine patients in a headache clinic is 25%.<sup>26</sup> Like other psychiatric comorbidities of migraine, PTSD has a higher prevalence in chronic migraine (43%) compared to episodic migraine patients (9%) but is associated with both.<sup>27</sup> This association may be linked to brain serotonergic function since both migraine and PTSD concern serotonergic dysfunction. It is interesting to note that PTSD and Migraine share many comorbidities such as depressive and anxiety disorders.<sup>28</sup>

### ***Abuse***

Studies have shown that abuse in both childhood and adulthood is associated with higher rates of migraine. Specifically, childhood trauma, defined as both abuse and neglect, occurred at higher rates in migraine patients, at 58% of the patient population. Abuse and neglect were defined not only by physical abuse and neglect but also by emotional abuse and neglect. Importantly, emotional abuse and neglect occurred in 38% of the patient population. Over 33% of migraine patients had higher rates of abuse during adulthood. Interestingly, prior substance abuse was associated with physical and sexual abuse and physical and emotional neglect. Current depression was associated with physical, sexual and emotional abuse, and physical and emotional neglect, while current anxiety was associated with all childhood abuse and neglect. The prevalence of emotional abuse among migraine patients was significantly higher than that reported in studies involving the general population.<sup>29</sup> The frequency of chronic migraine was higher in those reporting physical and emotional abuse, and emotional neglect. Migraine patients with a history of emotional trauma had higher frequencies of daily continuous headaches, severe headache related disability and symptoms of migraine associated allodynia than the non-abused cohort. They also developed migraines at an earlier age.<sup>30</sup> Depression and anxiety were strongly associated with each type of childhood maltreatment. This association became even stronger when more than one type of maltreatment occurred. Even controlling for anxiety and depression, childhood emotional abuse was still strongly associated with headache frequency.<sup>29</sup>

## **Substance Abuse**

Substance abuse and migraine are associated. When people with migraine are prescribed narcotics there is an increased risk for abuse and addiction. A study revealed that 19% of opioid dependent patients started opioids because of headache.<sup>31</sup> Patients with both medication abuse and chronic migraine have a greater risk of chronification, a poorer quality of life, and are harder to treat than patients without chronic migraine and medication abuse. One study revealed that 7% of migraine patients used injections of morphinomimetic drugs at least once weekly and were considered drug abusers by their doctors.<sup>32</sup> Another study found that drug abuse was a concern in 19% of migraine patients who returned to the emergency department (ED) three or more times in four months.<sup>33</sup> Interestingly, people with migraine who were most likely to be prescribed narcotics in the ED were triaged as less urgent and reported allergies to medications. It has been suggested that physicians may prescribe narcotics in the ED to avoid confrontation with the patient.<sup>34</sup> Tornabene et al. found that compared to patients with migraine who visited the ED once, patients who visited the ED multiple times were more likely to receive opioids as treatment, get multiple doses of the opioids, and be given opioids as the first pharmacological treatment.<sup>35</sup> In addition, they found that the patients who received first line narcotics were more likely to return to the ED with a headache within 7 days, raising the question of whether the treatment lacked efficacy or whether they were drug seeking.<sup>36</sup> One study found that of patients with chronic migraine and medication overuse, 20-40% relapsed into medication overuse within 1 year after detoxification. The patients who relapsed reported higher anxiety and depressive-like symptoms than those who did not relapse. This emphasizes that there is a complex association with psychiatric comorbidity. The National Comorbidity Survey Replication (NCS-R), a cross sectional US population based survey of mental disorders, found that the lifetime prevalence of drug abuse was greater in episodic migraine patients (11.2%) compared to people without headache (7.3%). However, in this study, when they controlled for depression and PTSD, the association between substance abuse and migraine was no longer significant.<sup>37</sup>

## **Sleep**

Migraine patients often present with sleep complaints, and studies have found that many migraine patients suffer from sleep disorders. There have been studies linking migraine with sleep disorders parasomnia and sleep breathing disorders but recently, studies have also investigated sleep disorders such as Restless Leg Syndrome, periodic limb movements, and narcolepsy.<sup>38</sup> One study found that the lifetime prevalence of Restless Leg Syndrome in migraine patients is 17.3% compared with 5.6% in the general population.<sup>39</sup> A population-based study in Taiwan has shown that adults with nonapnea sleep disorders are at a higher risk of developing migraine.<sup>40</sup> There is still debate if insomnia is a risk factor for migraines.<sup>41</sup> It is also unclear to what degree medications commonly used to treat migraine impact sleep disorders since both share physiological processes.<sup>42</sup>

## **CONCLUSION**

Psychiatric comorbidities are more common in migraine patients than in the general population, and they are a risk factor for migraine chronification. Further research is needed to better understand the mechanisms for the association and to learn to how best treat these patients.

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