

# Expert Opinion

## Migraine, Psychiatric Comorbidities, and Treatment

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Caring for patients with more than one condition is often a challenge, particularly when those conditions cross over into other fields of medicine. Depression, anxiety, and bipolar illness are common problems which may complicate the diagnosis and treatment of many of our migraine patients.

### INICAL HISTORY

A 28-year-old woman has had migraine without aura since the age of 13 with attacks now occurring about 4 times per month with an inconsistent response to triptans. In addition, she has had recurring endogenous depression for 3 years treated with paroxetine last over one year ago with some help. Her depression is currently mild. There is no history to suggest hypomania or mania. She has been frequently anxious for a few years as well, worrying about everything, which can cause difficulty falling asleep. Her mother has a history of major depression and migraine. Her sister is being treated for migraine and bipolar disease.

### QUESTIONS

Is migraine co-morbid with psychiatric disorders?  
Is there a genetic basis?

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Does the psychiatric disorder (eg, depression, anxiety, and bipolar disease) precede or follow the onset of migraine?

Is depression more prevalent in those with chronic migraine as compared with those with infrequent migraine?

Should the psychiatric disorder alter the treatment of migraine?

What preventive medication would be helpful in this case?

What about for migraine and bipolar disease?

### EXPERT OPINION

One of the major reasons that patients come to see headache specialists is due to failure to respond to typical treatment. If her initial diagnosis is accurate but she has not responded to typical treatment, often, her primary care physician, family practitioner, or obstetrician/gynecologist will refer her to more specialized care. The aspects of failure to respond most likely include increasing frequency of headache, increased disability from pain and associated features, lack of adequate acute relief from medication with prolonged, disabling attack and higher migraine index ratings. Complicating features of care include unclear diagnosis of headache, secondary headaches, side effects from medications, and comorbid illness.

In this case, the patient in question presents with a history of depression not otherwise specified, anxiety disorder not otherwise specified, insomnia, and fairly frequent migraine with poor response to

treatment. Her care requires understanding of the relationship between her multiple diagnoses and treatment options.

**Is Migraine Co-Morbid With Psychiatric Disorders? Is There a Genetic Basis?**—Over 50% of those people in the general population with migraine never receive the diagnosis.<sup>1</sup> Of those diagnosed and referred to specialists, rates of comorbid illness may reflect a much higher rate than the general population. However, that being said, there is a moderate body of evidence over the past 50 years for significant mood and anxiety disorders in the general population with migraine as well as in specialists' offices.<sup>2-4</sup>

Studies suggest that the odds ratio between migraine and major depression are between 2.2 to 4.0.<sup>5</sup> Furthermore, those patients with migraine with or without major depression are at a higher risk of suicide than those without migraine.<sup>6</sup> Patel et al compared the prevalence of depression in migraine, probable migraine, and control patients and showed a prevalence of 28.1%, 19.5%, and 10.3%, respectively.<sup>7</sup> Breslau et al demonstrated over a 2-year period that depression raised the incidence of migraine and presence of migraine raised the incidence of depression.<sup>8</sup> A cross sectional analysis by Zwart et al of 50,000 people suggested that increased frequency of migraine was predictive of a higher incidence of both depression and anxiety disorders.<sup>9</sup>

Bipolar disorder also appears to be far more common in the migraine population. Bipolar I disorder had an odds ration of 2.4 in patients with migraine without aura and 7.3 among patients with migraine with aura.<sup>10</sup> Bipolar II had an odds ration of 2.5 in the migraine without aura group and 5.2 in the migraine with aura population.<sup>10</sup>

Among anxiety disorders, migraineurs appear to be at 4 to 5 times greater risk for generalized anxiety disorder and 5 times more likely to suffer obsessive compulsive disorder.<sup>11</sup> However, other studies found different results in an older population.<sup>12</sup> Panic disorder occurs from 3 to 10.4 times more common among migraineurs than the general population – particularly among those with migraine with aura.<sup>13</sup> Again, there appears to be a bidirectional association as migraine increases the risk of panic disorder and Panic increases the risk for the onset of migraine.<sup>14</sup>

The genetic relationship between migraine and psychiatric disorders is an interesting one to speculate about as little data exist to support this. Currently, the only genes that we know represent only a small percentage of patients with migraine with hemiplegia and are not necessarily representative of the average migraine patient. Current studies are ongoing to attempt to gain greater knowledge of the genes involved. Similarly for mood disorders, very little definitive work has been done to elucidate genes involved. Epidemiology does provide some clues in that the incidence of migraine is much greater among first degree relatives of migraineurs and incidence of depression and anxiety much greater in first degree relatives of those suffering from those illnesses.<sup>15</sup> Furthermore, those neurotransmitters that are most likely involved in migraine including serotonin, dopamine, and norepinephrine are also involved in the pathogenesis of mood and anxiety disorders. This remains an area for further research and no definitive genetic relationship can be put forth at this time.

**Is Depression More Prevalent in Those With Chronic Migraine as Compared With Those With Infrequent Migraine?**—As headache frequency increases the risk of depression and anxiety also appears to increase. Chronic daily headache has greater comorbidity than episodic migraine.<sup>16</sup> In fact, chronic daily headache patients may have over 90% chance of comorbid psychiatric disorder.<sup>17</sup> Some research suggests that anxiety disorders may be negative prognostic factors as this raises the risk for migraine and depressive disorder further down the road.<sup>18</sup> While one would suspect that the presence of comorbid psychiatric disorder would predict a poorer outcome, there is little in the literature to support this. This may be due to a number of biases, including that those with complicating comorbid disorders end up at headache specialty centers where more time and resources are devoted to helping those individuals.

**Does the Psychiatric Disorder (eg, Depression, Anxiety, and Bipolar Disease) Precede or Follow the Onset of Migraine?**—Anxiety disorders tend to precede the age of onset of depression and migraine and there has been historical speculation that the disorders may represent a continuum.<sup>19</sup> The mean age of onset for anxiety is 12 years, the mean age of onset for

migraine is 15 years, and the mean age for depression is 17 years.<sup>20</sup> There is no clear relationship between new episodes of major depression and migraine attack frequency. While it is common to see adjustment disorder with depressed features in response to stressful life circumstances (such as illness), that do not seem to translate into attacks meeting the criteria for major depressive episodes. In essence, the relationship between mood disorders and migraine is bidirectional with either potentially being the initial presentation in the individual being treated.

**Should the Psychiatric Disorder Alter the Treatment of Migraine?**—Patients with migraine and comorbid depression, anxiety, and bipolar illness often require individualized treatment. It is a good rule of thumb to think that medical treatment of migraine should be tailored both to the individual attack and also to the individual. Modification of treatment may play a role with considerations of preventive management and also, potentially abortive treatment.

When considering preventive care, the physician often makes the decision based upon the migraine subtype, relative drug efficacy, patient preference, adverse event profile, and coexisting conditions.<sup>21</sup> The decision for which pharmacotherapeutic agent to use may be influenced by relative efficacy in treating the comorbid condition, or risk of exacerbating that condition. Sometimes a single agent may be considered for multiple conditions. However, when it comes to trying to treat multiple conditions with one medication, the practitioner should use caution. While it may seem like a way to minimize medications, it may also lead to certain difficult situations. For example, if one condition is stable but the other is not, the dosage may require change and lead to destabilization of the stable condition. Additionally, in today's current healthcare climate, often an individual is followed by multiple practitioners. If they are splitting care, then multiple physicians may recommend medication changes leading to further confusion. If 2 separate medications are chosen then that may make it easier to treat each condition separately, but may increase the risk of drug interactions and raise the cost of care.

The choice of preventive medication can potentially complicate the care of psychiatric conditions.

There is reasonable evidence that suggests that B blocker agents may worsen depression.<sup>22</sup> Generally they can also cause fatigue, hypersomnia, and weight gain, which may also exacerbate some of the core components of depression. The use of certain antidepressants in a patient with underlying bipolar disorder may actually raise the risk of spontaneously triggering a manic (or hypomanic) episode. In some cases, the use of such agents has triggered manic episodes in individuals who have never manifested these traits prior. This has been referred to as "bipolar III" disorder and is an iatrogenic condition. So, the choice of preventive medication can have significantly negative outcome on comorbid conditions and needs close consideration.

Even abortive medications may need to be considered in a patient with comorbid migraine and psychiatric disorder. There is some suggestion of the risk of serotonin syndrome in patients using both selective serotonin reuptake inhibitor (SSRI) and serotonin norepinephrine reuptake inhibitor (SNRI) and triptan medications.<sup>23,24</sup> While the risk appears to be very low and a small number of case reports have actually been reported, this may represent an underreporting of the true incidence.<sup>25</sup> The evidence at hand suggests the risk is minimal and the question remains whether the prescribing physician should routinely warn the patient of the potential interaction.<sup>26</sup> For those patients on multiple serotonin agents with previous history of serotonin syndrome or with use of over the counter herbal treatments, the use of triptan drugs may be reconsidered and alternative acute therapies explored.

Pharmacotherapeutic options are not the only treatment for migraine. Evidence exists for the use of biofeedback, autogenic training, cognitive behavioral therapy, and other biobehavioral strategies.<sup>27</sup> In a patient with comorbid psychiatric conditions, these biobehavioral therapies may serve multiple roles in addressing the migraine and the other conditions. Many of these techniques have been used with the treatment of anxiety and mild to moderate depression.<sup>28</sup> In the patient with multiple conditions, the addition of these adjunctive therapies may significantly improve medication adherence and outcome.

**What Preventive Medication Would Be Helpful in This Case?**—Antidepressant medications fall into several different groups: tricyclics, SSRIs, SNRIs, norepinephrine dopamine reuptake inhibitors, monoamine oxidase inhibitors, and atypical or other medications. The relative potency and efficacy of these medications with regards to their antidepressant effect is the matter of much debate. Some studies suggest that the newer agents are not necessarily more effective, but have a lower incidence of side effects, leading to improved compliance with treatment and greater patient satisfaction. Similarly, many of these medications also demonstrate anxiolytic effects of varying degrees. A number of these medications have been studied with regards to migraine prevention with a range of efficacy as well.

Among the tricyclic antidepressants, amitriptyline is the best researched migraine preventive,<sup>29-31</sup> although evidence exists for other tricyclics including imipramine, doxepin, nortriptyline, and desipramine.<sup>32,33</sup> Studies suggest that amitriptyline is at least as effective as propranolol and separates significantly from placebo with an average of 60-75% response rate<sup>34</sup> (defined as a decrease of greater than 50% of attacks). In one study, the addition of an SSRI made no difference in efficacy.<sup>35</sup> Most likely the mechanism of action is by means of a decrease in serotonin synthesis in the brainstem raphe nuclei, although the effect on norepinephrine also may play a role.<sup>36</sup> Tricyclics are sometimes referred to as “dirty” medications due to the effect on other neurotransmitters including acetylcholine, histamine, and alpha-1-adrenergic effects. While these may account for efficacy they also cause significant side effects. The anticholinergic effect may lead to sedation, dry mouth and eyes, and urinary retention. The antihistamine effect may also lead to sedation, and the alpha-1-adrenergic effect may cause orthostatic hypotension. So, while the greatest evidence for migraine prophylactic efficacy lies with the tricyclic medications, they also have limiting side effects.

Selective serotonin reuptake inhibitors have also been studied but without the brisk results of the tricyclic medications. Fluvoxamine,<sup>37</sup> fluoxetine,<sup>38-40</sup> and citalopram<sup>41</sup> have the most data but have relatively low efficacy. This may be different when treating

chronic migraine and chronic tension type headache. Expanding to studies including multiple pain types shows greater efficacy when combining different pain syndromes. The SSRIs have very low rates of adverse events and have become the gold standard for treatment of typical major depression, but unfortunately have a limited role strictly for the prevention of migraine.<sup>42,43</sup>

There are currently 2 SNRIs – venlafaxine and duloxetine. These differ from the SSRIs by having a greater affinity for norepinephrine receptors and less so at the serotonin receptor.<sup>44</sup> To date, there have not been any significant studies with the use of duloxetine for migraine prevention. However, there are some efficacy data utilizing venlafaxine – a phenyl ethylamine.<sup>45-47</sup> In a crossover, blinded comparison study to amitriptyline, venlafaxine demonstrated equivalency of effect over a 12-week period and separation from placebo.<sup>48</sup> The rate of adverse side effects was significantly lower for venlafaxine, with more patients discontinuing amitriptyline due to hypersomnia, concentration difficulties, and orthostatic hypotension. In another study, venlafaxine was compared with placebo in 60 patients over a 2 month period. Eighty percent of those patients receiving 75 mg evaluated the effect as good or very good, and 88% of those receiving 150 mg evaluated the effect as good or very good.<sup>49</sup> While further large studies are necessary, these preliminary data are favorable.

Some limited data exist for other antidepressants. The mono amine oxidase inhibitors (including phenelzine, tranylcypromine, and selegiline) have been used for migraine prevention historically, but are of extremely limited use due to severe adverse events. Most common is hypotension, but most severe is the “tyramine reaction” caused by small mono amines, which can lead to malignant hypertension, seizure, coma, and death.<sup>50</sup> The use of MAO-Is requires a very strict diet to which most patients are unable to adhere. Mirtazapine has also shown some promise in low doses, but further data are required as this is mostly from individual case reports.<sup>51</sup>

Given the relative efficacy of the antidepressants and their different adverse event profiles, one can make an argument for the use of several different medications in this patient. The question as to appro-

appropriate first line antidepressant therapy and augmentation strategies is beyond the scope of this article and instead we will focus on the migraine prevention efficacy. Given her insomnia, anxiety, and depression, one could make an argument for the use of a tricyclic antidepressant (such as amitriptyline) as the side effect of sedation may be helpful for her insomnia in the short term. However, the risk of weight gain should be discussed with the patient (particularly as a young woman). On the other hand, venlafaxine has a lower incidence of adverse events, greater tolerability, and perhaps equivalent effectiveness for depression, anxiety, and migraine prevention. This may ultimately prove a better choice in this young woman with only moderate active symptoms of depression and with a moderate migraine disease burden.

**What About for Migraine and Bipolar Disease?**—Considerations for bipolar disease may have a significant change in our choice of medication. The fact that this patient has a first degree relative with bipolar illness raises her risk above that of the general population. The unrestricted effect of an antidepressant therapy has the risk of uncovering the bipolar diathesis and leading to a hypomanic or manic episode. This would require significant alteration in pharmacotherapy. Several medications used for bipolar treatment have also been used for migraine therapy.

While lithium is the most common treatment for bipolar maintenance, it does not appear to be effective for migraine prophylaxis. However, it may be of use in some other headache conditions including hypnic headache. It has significant cardiac, renal, and thyroid side effects and requires close monitoring of blood levels particularly in an aging patient.

Sodium valproate has been used over the last several decades for both bipolar maintenance and for migraine prophylaxis. In double blind, placebo controlled studies, it has consistently shown good effect as a preventive treatment for migraine.<sup>52</sup> However, sodium valproate also has a significant adverse event profile with complications including weight gain, lethargy, hair loss, hepatic effects, birth control interactions, and teratogenicity. It needs to be used with caution in patients who may experience childbirth, and numerous patients are reluctant

to start treatment due to concerns over these adverse events.

Lamotrigine has been demonstrated to be effective predominantly for the depressed side of bipolar disorder and has been enjoying increased clinical popularity. One study suggested that lamotrigine may have utility in the prophylaxis of migraine with aura, but little evidence exists for its use in typical migraine cases.<sup>53</sup> The most severe side effect may be the risk of Stevens–Johnson syndrome and the patient needs to be aware of any new onset rash while using lamotrigine.

The most recent mood stabilizers are the atypical neuroleptics or antidopaminergics, some of which have recently been approved for the acute treatment of bipolar illness (including risperidone, olanzapine, and aripiprazole). There are limited data available for their use in the prophylaxis of migraine but there have been some small series and case reports suggesting that there may be benefit.<sup>54</sup> They have enjoyed an increase of use in headache specialty clinics and assuredly should receive greater scrutiny in the future. While their side effect profile is much better than the older “typical” neuroleptics, there are still significant risks with use including movement disorders, cognitive side effects, and the metabolic syndrome incorporating weight gain, elevated cholesterol, and risk for diabetes.

Given the existent data, if we are considering bipolar illness in our patient, then we may be best served by considering the use of sodium valproate with concurrent use of birth control.

While this article may provide some general guidelines to care, the determination of prophylaxis should be tailored to both the individual and to the attack. Ignoring the coexistence of psychiatric disorders in migraine sufferers may limit the ability to treat someone appropriately and effectively. Even after the initial drug selection is made, adjustments may need to be made, fallback strategies considered, and adverse events monitored.

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