NEW INSIGHTS INTO THE COMORBIDITY OF MIGRAINE AND DEPRESSION

ABSTRACT

Migraine has been shown to be comorbid (ie, occurring together more often than by chance) with several disorders, including depression, panic disorder, and epilepsy. Migraine and epilepsy appear to share some common etiologic mechanisms because antiepileptic drugs are used to prevent migraine recurrences. Many researchers have focused on the relationship between migraine and depression, in part because both are so common in women. It is not yet clear whether depression is a psychological response to migraine and/or if those with depression are at greater risk for developing migraine. This article summarizes a previously published study to determine the directionality between depression and migraine, and depression and severe headache. The results show that migraine and depression are bidirectional, each increasing the risk and persistence of the other. Severe headache and depression appear to have a unidirectional relationship—depressed patients are not at increased risk for severe headache, but severe headache patients are at increased risk for depression. These results affect therapeutic strategies for migraineurs and may help researchers to focus on the cause of migraine and depression. (Advanced Studies in Medicine. 2002;2(21):754-757)

The comorbidity of depression with migraine has been known for more than a decade. Several investigators have looked into the epidemiology of these 2 disorders as well as the directionality of their relationship (ie, the presence of migraine increases risk for depression onset or more severe depression vs the presence of depression increases the risk for migraine or more severe migraine).

Migraine appears to be comorbid with several psychiatric disorders, in particular, anxiety disorders. A causal relationship for the anxiety disorders has not been identified (eg, having migraines makes a patient more anxious), which raises the possibility of common biochemical mechanisms, genetic factors, and/or environmental influences.

The strongest etiologic link between migraine and a comorbid disorder is observed with epilepsy. Antiepileptic drugs are used as effective prophylactic migraine treatment, suggesting common mechanisms in epilepsy and migraine. Genetic studies also suggest a link between epilepsy and some types of migraine.

The comorbidity of depression with migraine has received the most attention for several reasons. First, the prevalence of migraine is relatively high, especially in women, and women are more prone to depression. Great attention has also been given to the disability associated with migraine, and depression also causes significant disability. Lipton et al examined the effect on health-related quality of life in comorbid migraine and depression and found, not surprisingly, that quality of life was significantly reduced in subjects with comorbid migraine and depression—even more so than with either condition alone.

A recent study sought to examine possible causal pathways between the 2 disorders to determine if a
bidirectional relationship exists (ie, the presence of migraine causes an increased risk for depression and the presence of depression causes an increased risk for migraine). Other severe types of headache were also analyzed for their relationship to depression.15

A computer-assisted telephone interview was used to screen almost 4765 people ages 25 to 55 years in the greater Detroit, Michigan, area for the presence of migraine or other severe types of headache. The interview instrument was developed by Lipton and Stewart and was validated against clinical examination.16,17 Respondents were asked if they experienced at least 1 headache in the past year not due to illness, hangover, or head injury, and used the International Headache Society criteria to determine if the headaches were migraines. Nonmigraine severe headache was defined as lasting 4 to 72 hours, no history of the hallmark signs of migraine (ie, nausea, vomiting, and phono- or photophobia associated with headache), and a score on the Headache Impact Test-6 (HIT-6) that was at least one third of the score required for migraine. (HIT-6 measures pain and disability associated with headache.) The use of the hallmark migraine signs was used in the severe-headache group to eliminate those with “migrainous disorder not fulfilling migraine criteria.” The same type of inquiry was made about the second most severe headache type if more than 1 type of headache was reported.

In total, 1696 respondents were eligible to continue in the study: 683 with migraine in the past year, 253 with severe headache in the past year, and 760 sex- and age-matched controls to the migraine group who never had a headache with pain intensity above 2 on a scale of 1 to 10.

In a face-to-face interview, participants were also questioned about the lifetime prevalence of depression. Of 1696 original participants, 1287 (76%) took part in the face-to-face interviews. The American Psychiatric Association criteria for major depression are outlined in Table 1.18

The demographics among the 3 groups varied slightly in terms of sex and education. The migraine group had the most women (83%) compared with the severe headache group (54.8% women) and the control group (76.8% women). The control group had a higher proportion of college graduates. Otherwise, the demographics of the 3 groups were similar. The estimated mean values in the groups were as follows: age, 40 years; race, 72% white, 22% black, and 4% other; and education, 5% less than high school, 31% high school, 33% some college, and 30% college.

The results show that the lifetime prevalence of depression with migraine was similar to that with severe headache (Table 2). Interestingly, migraine with aura sig-

### Table 1. DSM-IV Criteria for Major Depression

<table>
<thead>
<tr>
<th>Requirement</th>
<th>DSM-IV = Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Adapted with permission from the American Psychiatric Association.19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requirements for diagnosis: &gt;5 symptoms during the same 2-week period with at least 1 symptom being depressed mood or diminished interest or pleasure.</td>
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</table>

#### Table 2. Lifetime Prevalence of Major Depression in the Migraine, Severe-Headache, and Control Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Major Depression (%)</th>
<th>Sex-Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>40.7</td>
<td>3.51 (2.64-4.64)</td>
</tr>
<tr>
<td>W th aura</td>
<td>49.4</td>
<td>4.90 (3.34-7.19)</td>
</tr>
<tr>
<td>W thout aura</td>
<td>37.0</td>
<td>3.03 (2.23-4.11)</td>
</tr>
<tr>
<td>Severe headache</td>
<td>35.8</td>
<td>3.18 (2.14-4.73)</td>
</tr>
<tr>
<td>Controls</td>
<td>16.0</td>
<td>1.00</td>
</tr>
</tbody>
</table>

CI = confidence interval. 
Reprinted with permission from Breslau et al.15
significantly increased the odds of the first episode of depression compared with migraine without aura ($P = .013$). In the majority of migraine cases, the onset of headache preceded the onset of major depression.

To examine whether one disorder influences the presentation of the other, sex-adjusted hazard ratios were calculated between migraine and depression (Table 3). Of note, education was inversely related to the onset of migraine but did not influence the hazard ratio. The difference in risk of depression between migraine with and without aura was not significant; however, in the reverse direction, those with a history of depression had a much higher risk of migraine with aura compared with migraine without aura.

Regarding severe headache, the relationship is more unidirectional, with a history of severe headache having a greater influence on the onset of depression than the reverse scenario. The odds ratio of first onset of major depression was not affected by sex or education. Sex had no effect on the risk of first occurrence of severe headache in patients with a history of depression. Therefore, migraine influences the first onset of major depression and major depression influences the first onset of migraine, particularly migraine with aura—the relationship is bidirectional. However, this bidirectional relationship is not observed between depression and severe headache.

The specific bidirectional association between migraine and major depression suggests a common etiology. Depression does not appear to be an emotional or psychological reaction to the burden of migraine.

A specific bidirectional relationship has also been observed between panic disorder and migraine/severe headache. However, panic disorder is not uniquely associated with migraine (ie, the prevalence is also higher in those with other severe headache types). Migraine and severe headaches pose an increased risk for first onset of panic disorder, and panic disorders pose an increased risk for first onset of migraine or other severe headache type, but the effect of the latter is not as strong. Further research into the mechanisms behind major depression, panic disorder, and migraine will hopefully provide clues to the etiologies of all 3 disorders.

Further data on the relationship between migraine/severe headache and major depression will be published in the near future.

### REFERENCES


### Table 3. Directionality of Influence Between Migraine and Major Depression

<table>
<thead>
<tr>
<th>Previous Disorder</th>
<th>First Onset of:</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>Depression</td>
<td>2.35 (1.84–3.01)</td>
</tr>
<tr>
<td>Major depression</td>
<td>Migraine</td>
<td>2.75 (2.17–3.48)</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>Depression</td>
<td>2.81 (1.95–4.04)</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>Depression</td>
<td>2.18 (1.65–2.88)</td>
</tr>
<tr>
<td>Depression</td>
<td>Migraine with aura</td>
<td>3.98 (2.70–5.86)</td>
</tr>
<tr>
<td>Depression</td>
<td>Migraine without aura</td>
<td>2.22 (1.65–2.98)</td>
</tr>
<tr>
<td>Depression</td>
<td>Severe headache</td>
<td>1.63 (0.94–2.83)</td>
</tr>
<tr>
<td>Severe headache</td>
<td>Depression</td>
<td>3.56 (2.38–5.32)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
Adapted with permission from Breslau et al.