BACKGROUND
TAS is a 38-year-old woman with migraines without aura since age 16.

In the early years, migraines occurred 2 to 3 times/month, lasted 8 to 12 hours, and were partially relieved with over-the-counter analgesics. In the past 5 years, the migraine frequency has increased to 2 times/week, lasting 1 to 3 days. In addition, she has a headache “24/7” that is bilateral and of mild-to-moderate intensity. The patient describes herself as “a prisoner of my migraines” stating, “I have no life. I can’t travel. I can’t go on vacation, because I’m going to get sick with a migraine. My kids are upset, because I’m never at their soccer practices.” She has been treated with triptans and was recently started on amitriptyline 25 mg at bedtime for headache; however, her personal and social life continues to be affected. She misses an average of 1 to 2 days of work/month and is afraid she will lose her job. Her coworkers seem resentful of her frequent absences from work.

MEDICATIONS
The patient takes the following medications for management of her headaches and comorbid symptoms: sumatriptan 100 mg when needed for acute migraine, alprazolam 0.25 mg when needed for anxiety, and amitriptyline 25 mg at bedtime for headache prevention. (Note: The patient is taking sumatriptan for acute treatment, but is not on any type of rescue therapy, which is frequently the case when patients are referred from primary care practitioners.)

PERSONAL AND SOCIAL HISTORY
TAS has been married for 15 years. She lives with her husband and 2 children, aged 10 and 8 years. Her husband thinks she is “a big baby” and wishes that she would “buck up.” She also has lost friends as a result of her constant headaches, and as previously mentioned, her job is being threatened by her symptoms. She works as a loan officer at a bank. TAS rarely drinks alcohol; she has an occasional beer or glass of wine (1 serving) and does not drink on a daily basis, because she knows it will precipitate a headache. She has been...
smoking 1 pack of cigarettes/day for 15 years. (Note: Loss of employment is a poor prognostic sign for migraine. Patients frequently present to headache specialists when their job is threatened or when they have had to go on disability because of the inability to work.)

**Family History**

There is a family history of headaches. The patient’s mother had “sick” headaches, and her sister has “sinus” headaches. She has a brother who has been diagnosed with major depression. Her father has hypertension. (Note: If there is no family history of migraine, this should be a red flag to look carefully for other causes of headache. Often the history of migraine in the family is obscured by the long-standing impression of the lay person that headaches are “sinus” or “sick” headaches.)

**Review of Symptoms**

Psychiatric review of symptoms is positive for anxiety, and she worries about the impact of her migraines on her family. According to TAS, she does not sleep well (the migraines wake her up at 2:00 AM or 3:00 AM), and her mood is “really depressed.”

Gynecologic review of symptoms reveals that her menstrual periods are regular; her husband had a vasectomy, therefore, she does not use any form of contraception. (Note: Whereas women often attribute mood and headache disorders to hormonal issues, in most instances these are separate problems. Menopause is an innocent bystander, so to speak, which is supported by the fact that men present with transformed migraine [TM] at approximately the same age as women.)

**Physical Examination**

General examination reveals obesity with a body mass index of 28 kg/m². Neurologic examination is normal, except that she is frequently tearful and sad throughout the entire interview.

**Discussion**

**Dr Johnson:** In terms of her diagnosis, we have already talked about the problems that we have with classification. TAS clearly has migraine without aura on 8 to 10 days of the month. She also has a daily tension-type headache (TTH) on 20 to 22 days a month. According to the second edition of the International Classification of Headache Disorders (ICHD-II) criteria, she has migraine without aura and chronic tension-type headache (CTTH). She does not meet the ICHD-II criteria for chronic migraine because she does not have 15 or more migraine-days/month. However, I would use the term “transformed migraine” because the daily headache pattern evolved from migraine without aura. She also has anxiety, depression, obesity, and tobacco abuse.

In reviewing the epidemiologic literature, whereas there is a large body of knowledge about migraine and depression, there is very little about CDH and depression (the literature is still young). Affective disorders, such as major depression and generalized anxiety disorder, are 3 times more common in persons with migraine than among the general population. Possible associations are described with bipolar disorders and substance abuse. However, it is important to recognize that many patients with migraines do not have comorbid psychiatric disorders, and we need to be aware of the stigmatization of people with headache.

**Dr Rothrock:** Doesn’t it strike you as interesting that migraine is comorbid with positive conditions, such as epilepsy, panic disorder, bipolar disorder, anxiety disorders, and also with the so-called negative disorder of depression? If the underlying problem is brain hypersensitivity, then the other disorders make sense. Why depression?

**Dr Johnson:** That’s a good question, and I don’t think we know the answer. If you have chronic pain, then one would expect reactive depression, but what about major depression? Breslau et al demonstrated in an epidemiologic study the 3-fold increased association between migraine and depression. Then in a later study, Breslau et al attempted to answer the question, “Which comes first, the chicken or the egg—the depression or the migraine?” In other words, what is the direction of the association? A cohort of persons aged 25 to 55 years with migraine (n = 496) or with other headaches of comparable severity (n = 151) and control subjects with no history of severe headaches (n = 539) randomly selected from the general community were studied over a 2-year period. Major depression at baseline predicted the first-onset migraine during the 2-year follow-up period but not other severe headaches. Likewise, migraine at baseline predicted the first-onset major depression during follow-up, although the prospective association from other severe headaches to major depression was not significant. In other words, there was a bidirectional association between migraine and depression with each disorder increasing the risk for first onset of the other, but this phenomenon was not observed in relation to
other severe headaches. This would suggest a common underlying biologic basis for migraine and depression.

Furthermore, the association between migraine and depression seems to transcend all age groups. In an epidemiologic study of young adults, Merikangas et al. found an association between migraine and affective disorders, such as depression, generalized anxiety, panic disorder, social phobias, and possibly bipolar disorder. In a population older than 65 years, Wang et al. determined that there was a high comorbidity of depression associated with migraine or CTTH in the elderly, and the more recent and active the migraine condition was, the greater the association.

It is important to note that most of these are data for patients with migraine, not individuals with CDH. Evaluating CDH and psychiatric comorbidity is more difficult, because there is a limited body of literature. In a clinic-based study, Juang et al divided 261 patients with CDH into those patients with TM (58% of patients in this population, including those who had migraine and now had CDH) and the 35% of the population who had no history of migraine (diagnosed with CTTH). The psychiatric comorbidity was very high (higher than you see in populations of patients with migraine), with 78% of the patients with TM and 64% of the patients with CTTH having a psychiatric diagnosis, including major depression, dysthymia, panic disorder, and generalized anxiety disorder. The frequency of anxiety disorders was significantly higher in patients with TM versus CTTH (P = .02). The authors concluded from this investigation that patients with TM are at higher risk of psychiatric comorbidity.

Of course, there are many social and psychologic consequences of living with chronic pain, and we know that job and social relationships are affected negatively by episodic pain that becomes chronic. Among these consequences are sleep disturbances, decreased libido, sexual dysfunction, low energy, and poor concentration—all of which may contribute to depression, as evidenced by diminished energy, appetite, and ability to concentrate among those patients who have chronic, frequent, and repeated migraine attacks. Specifically, the data suggest that frequency, but not severity, of attacks predicts depression in patients with migraine. In 1999, Mitsikostas and Thomas reported the clinical profile of patients with primary headache syndromes who also suffered from mood disorders. Among 476 subjects, the average scores of the Hamilton rating scales for anxiety and depression were significantly higher in patients with headache (17.4 and 14.2, respectively) than in controls (6.8 and 5.7, respectively). Furthermore, higher attack frequency correlated with higher ratings of anxiety and depression. Lipton et al. also addressed frequency and severity of migraine attacks and the relationship to quality of life in a population-based study of 389 patients with migraine and 379 nonmigraine controls. The investigators used a health-related quality of life (HRQOL) screening tool and a mental health screening tool that involved a scale of depression. Migraine and depression were highly comorbid (2.7, 95% confidence interval, 2.1–3.5), and after adjustment for sex, age, and education, both were independently associated with decreased scores on the screening tools. Decreased scores on the mental health component of the HRQOL were correlated with higher attack frequency and greater disability.

Finally, with regard to the behavioral and psychologic aspects and management of TTH, one study by Holroyd randomized patients to stress management, amitriptyline, amitriptyline and stress management, or placebo. Among those patients who received stress management plus the tricyclic antidepressant (TCA), 64% were improved. Utilizing stress management alone, 38% of patients improved compared to those who only received placebo; 29% of these patients got better. Holroyd determined that, with high levels of anxiety or depression plus high headache severity and disability, the TCAs were superior. By contrast, if there were low levels of anxiety and depression, it did not make any difference whether patients took pharmacotherapy. This finding would suggest that there was an underlying depression that was being treated with the TCA.

Returning to the case of TAS, I started her on topiramate for preventative treatment. After 4 weeks, migraine attacks were down to once a week. They were of shorter duration, but daily headaches were continuing. She kept a headache diary, which I reviewed and found that every day was circled, although she felt “a little better.” After 12 weeks of treatment, TAS was down to 10 headache-days/month. I consider this to be a great response. Currently, she only has headaches 30% of the time versus 100% of the time, and she reports 3 migraine-days/month. Furthermore, her migraines are now less severe and responding to a triptan most of the time. She was instructed to take a second dose of the triptan after 2 hours if pain persisted and to add naproxen for rescue therapy when the triptan was ineffective. She has continued amitriptyline, because she seems to be sleeping well with it, and amitriptyline with an antiepileptic drug.
(AED) is often a good choice for preventative therapy in CDH. In the long run, if she gains weight I’ll take her off of the amitriptyline, because a negative body image may contribute to the depression.

I think that this a success story because although she still experiences headaches, her pain is manageable, and she can function. She is no longer tearful or sad. She has not missed any work. She feels a lot better. Thus, she is a patient in whom we did not address depression as a diagnosis, but rather her headache and her pain condition, and made her mood disorder better.

**Dr Rothrock:** Did she receive any benefit from the weight loss side effect of topiramate?

**Dr Johnson:** This particular patient has not, and that is why I will probably take away the amitriptyline. People gain weight, but sometimes if you use topiramate you can offset it. When patients come to me on a TCA, I will first get control of the headaches and then take away the TCA; that has been my approach. If they continue to experience depressive symptoms, I will use bupropion, because it doesn’t have weight gain and sexual dysfunction as side effects. Bupropion also may be beneficial as she sets a new stop date for cigarette smoking.

**Dr Forde:** Can I just make a point with amitriptyline? I use more nortriptyline because of the higher rate of side effects with amitriptyline. And although it doesn’t pertain to this patient, the American Medical Association states that amitriptyline is relatively contraindicated in patients aged 65 years or older.

**Dr Johnson:** If I’m starting the TCA, I also start with nortriptyline. We are in such a quandary in medicine right now because our feet are being held to the fire by insurance carriers and organizations to do evidence-based medicine. The evidence is for use of amitriptyline in headache, not nortriptyline.

**Dr Forde:** There is no evidence. A lot of clinical trials have been done, but none of the TCAs are approved by the US Food and Drug Administration for treatment of headache.

**Dr Rothrock:** There has never been a clinical trial—good or bad—for use of nortriptyline for migraines.

**Dr Johnson:** The data for amitriptyline were from the Holroyd CTTH study.10 At any rate, I totally agree with you that side effects are an issue and that the data are sparse. Furthermore, I don’t use TCAs if I can avoid it because of the weight gain.

**Dr Rothrock:** How do you know up front whether to treat concomitantly with a prophylactic agent for migraine plus an antidepressant? The amitriptyline dose used in this case is too low for treatment of depression.

**Dr Johnson:** I was primarily treating her sleep disorder by continuing amitriptyline that was started by her family doctor for headache; I decide whether to treat for depression depending on the history (eg, whether there is a history of depression treatment, including hospital admission for depression, suicide thoughts or attempts, or other benchmarks of major depression). When major depression appears to be a separate entity from the headache disorder, I will begin a treatment plan for depression. I may refer to a psychiatrist or initiate treatment. In cases such as this, when the patient says that her mood was fine until her headaches were like this, I often will begin with a headache preventative agent, often an AED, alone as first treatment. I will go that route, but if the patient’s headaches are responding to treatment and the mood is not improving, then I’ll treat the depression.

**Dr Forde:** I treat patients for pain management, and patients frequently say, “I have depression because I’m in pain all the time.” Once depression or anxiety is evident, you have to aggressively treat both conditions simultaneously—that is the depression and/or anxiety—in addition to the pain.

**REFERENCES**