

## Topiramate for Headaches

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Topiramate appears to be useful in the prophylaxis of several types of headache as these case histories illustrate.

### CLINICAL HISTORIES

**Patient 1.**—A 42-year-old woman presented with recurring headaches since aged 8. She has severe headaches about two times per month described as a generalized throbbing with nausea and occasional vomiting lasting up to 3 or 4 days, but she does not experience aura, or light or noise sensitivity. Triggers have included menses, hunger, alcohol, and smoke. Oral sumatriptan or rizatriptan often help. For the last 25 years, she has had mild, fairly constant, daily headaches which are a generalized or right- or left-sided aching without associated symptoms. She has been taking a few naproxen a week with mild help.

A magnetic resonance imaging (MRI) scan of the brain 12 years ago was normal. Over the years, she has been on propranolol and amitriptyline for prevention without benefit. She has tried biofeedback without help, and she exercises three times weekly. She tapered off butalbital with aspirin and caffeine (she was taking about 60 doses per month) on her own 6 months previously, and the headaches became less intense but still daily. Past medical history was negative. She drinks two cups of coffee or less daily. Neurological examination was normal. She is 5'4" and weighs 210 pounds.

The patient was started on topiramate, gradually increasing to 100 mg every 12 hours over 1 month. On follow-up after 1 month, she reported two severe headaches responding well to rizatriptan and two mild headaches responding well to tizanidine, 4 mg. Side effects included a decreased appetite with weight loss of 10 pounds, difficulty concentrating, and tingling of the hands and feet. On follow-up after 4 months, the headaches were even fewer with only one in the prior month responsive to rizatriptan. Her concentration seemed back to normal, but she had lost an additional 5 pounds and still had occasional tingling of the hands and feet.

**Patient 2.**—This 43-year-old woman fell 4 feet off a ladder 3 years prior and hit the back of her head on the floor without loss of consciousness. Ever since, she reported fairly constant, daily, bilateral nuchal-occipital and left more than right pressure without associated symptoms. She was taking two hydrocodone tablets daily, cyclobenzaprine, and etodolac without much help. Physical therapy also did not help. She had no complaints of memory problems, visual symptoms, or dizziness. She also complained of daily neck and low back pain without radicular symptoms. There was a prior history of only occasional mild headaches. Examination showed bilateral mid superior nuchal line tenderness and bilateral cervical paraspinal and superior trapezius tenderness. Neurological examination was normal. I performed bilateral greater occipital nerve blocks with xylocaine. She was placed on amitriptyline and baclofen and was advised to stop the cyclobenzaprine and taper off the hydrocodone.

On follow-up 2 weeks later, the headaches were no better. The dose of amitriptyline was increased,

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the baclofen was stopped, and she was started on ti-zanidine. Three weeks later, the headaches were less intense but still daily. She was started on topiramate, slowly increasing to 100 mg every 12 hours over 4 weeks. When seen 4 weeks later, the headaches were only occurring three times per week, and they did not require medication. However, the neck and low back pain were not improved. She had no side effects of the topiramate except for tingling of the fingers.

**Patient 3.**—A 21-year-old woman presented with a 1-month history of daily bifrontal and generalized pressure-type headache lasting a couple of hours and occurring three to four times daily. She was taking one hydrocodone tablet daily which dulled the headache. She was seen by an ophthalmologist and found to have mild bilateral disc edema with normal visual acuity and fields. An MRI scan of the brain was normal. She had been taking no medications before the onset of the headaches. She was 5'8" and 215 pounds. Neurological examination was normal except for mild disc edema of both eyes. A lumbar puncture produced an opening pressure of 28 cm H<sub>2</sub>O. Cerebrospinal fluid analysis was normal. Acetazolamide, 500 mg, twice daily was begun.

When next seen 2 weeks later, the headaches were still daily. She was trying to diet and exercise, but had lost no weight. She reported paresthesias of her hands and feet. The acetazolamide was discontinued, and she was started on topiramate increasing to 100 mg every 12 hours over 4 weeks. On follow-up 4 weeks later, she reported having no headaches at all for the prior 3 weeks. She had a decreased appetite and had lost 7 pounds. The paresthesias went away when acetazolamide was stopped and did not recur while on topiramate.

**Questions.**—Are the improvements described in chronic daily headache, posttraumatic headache, and pseudotumor cerebri likely due to placebo or topiramate? What is the evidence that topiramate is effective for these types of headache? Is weight loss a common side effect? What other types of headaches might respond to topiramate?

## EXPERT OPINION

These cases raise several questions about the use of topiramate in the treatment of difficult cases. First,

the easy part. There are, so far, two double-blind, placebo-controlled trials of topiramate published.<sup>1,2</sup> These include a monotherapy trial for migraine and a trial in which most patients were given topiramate as add-on therapy. Both trials showed statistically significant improvement in reducing headache frequency. Several other observational studies have shown improvement in migraine<sup>3,4</sup> and cluster headache.<sup>5</sup>

The first case concerns a woman with what appears to be transformed migraine, initially with episodic migraine and later daily headache with intermittent attacks suggestive of migraine. The second case is chronic posttraumatic headache. This is important because 80% of posttraumatic headache cases resolve by 6 to 24 months, after which the chances of improvement are slim. Case 3 is a case of pseudotumor cerebri.

That all three cases should respond to topiramate is consistent with my experience. Effective migraine medications are used to treat transformed migraine, although by general consensus this is a more difficult headache type to treat if the headache persists beyond 6 months or if it persists when overused abortive agents have been discontinued. There are very few studies on the prophylactic treatment of chronic posttraumatic headache, but many clinicians use migraine preventatives for chronic tension-type headache.

It could be that these are placebo responses, but it is unlikely. There are too few placebo-controlled trials in transformed migraine, posttraumatic headache, or pseudotumor cerebri to say what the placebo rate is for these disorders; however, I suspect it is very low in patients who have failed other treatments. The headache of pseudotumor may respond to pressure-lowering treatments, such as acetazolamide or furosemide, or to migraine treatments. Interestingly, topiramate is both a carbonic anhydrase inhibitor and a migraine preventative. Thus, it is a very attractive treatment for the headache of pseudotumor cerebri. Finally, the weight loss side effect is very attractive for patients with obesity and pseudotumor.

Various physicians use various dosing schemes. We start our patients at 15 mg or 25 mg per day and increase weekly in 15-mg to 25-mg increments, aiming for a daily dose of around 150 to 200 mg by the

2-month follow-up. After an average of 7 weeks of treatment with topiramate, our patients with migraine are on a mean of 150 mg per day and our patients with transformed migraine, a mean of 270 mg. Doses in other published studies vary from 100 mg to 325 mg per day. Topiramate is usually given in two daily doses but can be given once at night if patients are not on enzyme-inducing medications.

Weight loss is a common side effect of topiramate. In our first 37 patients, the average weight loss was 8 pounds over an average period of 7 months.<sup>6</sup> Similar findings are reported in other studies. Our patients who lose weight report early satiety, less hunger, and less snacking. There is evidence from animal studies that basal metabolic rate may increase.<sup>6</sup> In our experience, weight loss stops after 6 to 12 months, and some of the weight is regained.

The other common side effects are paresthesias, loss of taste for carbonation, and cognitive difficulties such as concentration problems, memory disturbances, and word-finding difficulties. The first two symptoms are due to the carbonic anhydrase inhibition and tend to fluctuate. Once informed, patients generally are not troubled by these side effects. The cognitive problems are minimized by starting at a very low dose (15 or 25 mg once daily) and increasing the dose by 15 to 25 mg per week very slowly. Within an individual they are dose-dependent and, if mild, will diminish in time. Occasionally, a mood disturbance may occur on topiramate—usually irritability or depression.

A rare but important side effect is the development of calcium oxalate renal calculi. One of my patients, who was greatly improved on topiramate, developed calculi and begged me not to take her off for this side effect. With the blessing of a urologist, she is continuing to take it. A few patients have developed cough or mild shortness of breath, some of whom needed to discontinue topiramate. We recently saw a patient develop hyperammonemic encephalopathy from the combination of divalproex sodium, topiramate, and butalbital.

Topiramate appears to be effective for cluster headache, both in a published series<sup>5</sup> and in my experience. It may be effective for trigeminal neuralgia,

and possibly atypical facial pain. It has been effective in a retrospective study of chronic tension-type headache.<sup>4</sup> There is one report that it works for SUNCT (short, unilateral, neuralgiform headaches with conjunctival injection and tearing). It may have an efficacy advantage over other preventatives: in relatively low doses (100 mg per day), it was effective in patients who had failed more than nine preventatives.<sup>7</sup>

In summary, topiramate is an effective migraine preventative. It appears to be effective for a broad range of headache disorders from transformed migraine to cluster headache. It has side effects in some patients, but they can usually be managed. It is an important new tool for the physician caring for patients with headache.

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