

Letter to the Editor

Modafinil Treatment of Excessive Daytime Sedation and Fatigue Associated With Topiramate

Sir: Over the past several years, the amount of research in the use of newer anticonvulsants in the treatment of bipolar disorder has increased.¹ Topiramate is one of those newer anticonvulsants, described in 1998 by Marcotte,² in the treatment of bipolar disorder. Vieta et al.³ indicate that adjunctive topiramate may be useful in the long-term treatment of bipolar spectrum disorders in the most difficult-to-treat patients. Most adverse effects of topiramate are related to the central nervous system and include sedation and fatigue.⁴ A case is presented in which a patient treated with topiramate for bipolar disorder who experienced sedation and fatigue responded favorably to modafinil.

Case report. Ms. A was a 33-year-old woman diagnosed with bipolar I disorder, most recent episode depressed, and amphetamine abuse, all in accordance with DSM-IV criteria.⁵ At the time of consultation, the patient was taking topiramate, 150 mg b.i.d., and venlafaxine extended release (XR), 150 mg once a day. She reported her general health as "good," did not use alcohol, had 6 months of methamphetamine abstinence, smoked 1-half pack of cigarettes daily, and drank 1 or 2 caffeinated sodas per day. She also denied the use of any herbal medications. Recent laboratory tests revealed a thyroid-stimulating hormone (TSH) of 2.54 μ U/mL, a complete blood count and comprehensive metabolic panel all within normal limits, a negative urine pregnancy test, and a urine drug screen negative for illicit substances.

In the past, she had been treated with lithium and valproate. Although the valproate had stabilized her condition, she experienced a 25-lb (11-kg) weight gain over the year preceding topiramate treatment. Ms. A had initiated the topiramate treatment about 6 months prior to consultation. She had noted a leveling of her mood aided by a prolonged abstinence of illicit substances as well as a modest decrease in weight. However, she continued to experience excessive daytime sleepiness and sense of fatigue, finding it difficult to stay awake at work, and had received negative commentaries from supervisors. Varying the dosage times did not seem to help, but the patient was unwilling to change the topiramate and venlafaxine regimen due to having reestablished a stabilized baseline condition.

Ms. A agreed to a trial of modafinil started at 100 mg/day for 1 week, then increased to 200 mg/day. She noticed a substantial decrease in daytime sedation with 1 week at the 200-mg dose. When she took one 300-mg dose, nervousness was a side effect, so Ms. A decided to continue at 200 mg/day. Ms. A also noted that because she was not experiencing daytime sedation, her fatigue lifted over the next several weeks. Her work performance improved to the point of receiving a raise and increased responsibility. Ms. A remains stable at 6 months; she continues

to take topiramate, 150 mg b.i.d., and modafinil, 200 mg on weekdays. Ms. A also remains addiction-free by attending a 12-step program.

Modafinil is approved by the U.S. Food and Drug Administration to treat excessive daytime somnolence associated with narcolepsy. It is chemically unrelated to other psychostimulants⁶ and is felt to alter the balance of γ -aminobutyric acid (GABA) and glutamate, resulting in the activation of the hypothalamus.^{7,8} It may also increase the metabolic rate in the contralateral nucleus, the central nucleus of the amygdala, and hippocampus.⁹ Modafinil has been used as an adjunct in the treatment of major depression, which allowed patients to achieve remission as well as targeting residual tiredness.¹⁰ Doghramji et al.,¹¹ in a 6-week, double-blind, randomized study, found an improvement in daytime sleepiness and fatigue in the modafinil-treated group of patients with major depression compared with the placebo group. DeBattista et al.,¹² in an open-label study, showed 14 of 20 patients with major depression "much improved" or "very much improved" on modafinil treatment in the management of fatigue and hypersomnolence. In a case report of 2 patients with schizophrenia, modafinil was used to treat amotivation and hypersomnia with no adverse effects.¹³ Rosenthal and Bryant,¹⁴ in a 4-week open-label study, demonstrated improvements in overall clinical condition and daily functioning in 11 schizophrenic patients receiving modafinil 200 mg/day.

Having benefited from topiramate despite the excessive daytime sleepiness and fatigue, modafinil was chosen because my patient did not want to change mood stabilizers. It was also chosen because modafinil does not appear to have the abuse potential of more traditional stimulants.¹⁵ Furthermore, patients with bipolar disorder treated with mood stabilizers have significant rates of noncompliance contributing to hospitalizations.^{16,17} In this case, it was felt that by treating the bothersome side effect of fatigue with modafinil, my patient's compliance would continue. Caution must be exercised in the interpretation of case reports, but modafinil may be a useful agent in treating somnolence and fatigue associated with topiramate. Further studies conducted in a more controlled fashion are encouraged.

Dr. Berigan reports no financial affiliation or other relationship relevant to the subject matter in this letter.

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