Extended-Release Bupropion-Induced Grand Mal Seizures

David J. Rissmiller, DO
Thomas Campo, DO

Bupropion hydrochloride is currently available in three formulations: immediate-release, sustained-release, and extended-release (ER). Several published reports exist concerning bupropion’s history of inducing seizures in both the immediate- and sustained-release formulations. Although the potential of the ER formulation for causing seizures is noted in the drug’s prescribing information, there is no previously published report of bupropion ER inducing seizures. In the case reported, a 27-year-old woman who was prescribed bupropion ER as well as clonazepam and lamotrigine (anticonvulsants), hydrocodone bitartrate (for irritable bowel syndrome), and zolpidem tartrate (for depression and associated anxiety and insomnia) experienced a grand mal seizure 6 months after beginning bupropion ER therapy. The patient was taken to the emergency department, where she had a second grand mal seizure 8 hours after the first one. Extended-release bupropion was discontinued, and the patient had not had additional seizures at 8 months follow-up.

Older tricyclic and monoamine oxidase inhibitor antidepressants have a dose-dependent potential to decrease seizure threshold. Alternatively, second generation antidepressants, particularly selective serotonin reuptake inhibitors, do not lower seizure threshold and may even have an anticonvulsant effect. In December 1985, the US Food and Drug Administration (FDA) approved bupropion hydrochloride, an immediate-release, monocylic antidepressant structurally related to amphetamines, as a second generation antidepressant.

Soon after the introduction of immediate-release bupropion (bupropion IR) on the market, patients taking the drug had higher rates of seizures compared with other second generation antidepressants. Most seizures occurred within the first 6 weeks of treatment. Seizures were especially prominent when patients took single doses greater than 150 mg or daily doses greater than 450 mg. The mean ingested daily dose in patients who had seizures was 8.3 mg per kilogram of body weight. In addition, electroencephalographic abnormalities (eg, epileptiform discharges) were reported in some patients on bupropion IR therapy.

At dosages of 450 mg/d or less, the incidence rate of seizures ranged from 0.35% to 0.44%, compared with a first-seizure incidence of 0.07% to 0.09% in the general population. The estimated seizure incidence was found to increase tenfold at dosages of more than 450 mg/d, and the number of seizure occurrences were twice as high in patients who took extra doses of bupropion IR on an “as needed” basis. In fact, a 2002 study reported that bupropion-induced seizures were the third most common cause of drug-induced seizures after cocaine ingestion and benzodiazepine withdrawal. In addition, about 21% of patients admitted with intentional bupropion overdose presented with seizures.

In 1996, the FDA approved sustained-release bupropion (bupropion SR) as an alternative to bupropion IR. Bupropion SR allowed for more convenient twice daily dosing and reduced seizure incidence rates to 0.1%. Published reports, however, warn that this long-acting formulation might prolong neurologic toxicity—including seizures in overdose.

Seven years later, in 2003, the FDA approved extended-release bupropion (bupropion ER) as a new, once daily substitute for bupropion IR and SR. Bupropion ER was never formally evaluated for seizures during premarketing clinical trials, and there have been no previously published cases of seizures in patients on the newer ER formulation. The current case reports an incident of two bupropion ER-induced seizures 8 hours apart in the same patient.

Report of Case
The patient was diagnosed with chronic irritable bowel syndrome in 1998 and was subsequently prescribed 2 oz of hydrocodone bitartrate syrup every other day. She continued this treatment for several years. In April 2004, the patient had her first major depressive episode. Her family physician prescribed the antidepressant mirtazapine, which caused substantial weight gain in the patient and was subsequently discontinued. Escitalopram oxalate was then prescribed but later...
discontinued because it caused diarrhea. The physician then prescribed bupropion ER 150 mg/d for 3 weeks, increasing the patient’s dosage to 300 mg/d in the fourth week. In addition, the patient’s physician prescribed the anticonvulsants clonazepam (0.5 mg twice daily) and lamotrigine (100 mg/d) as well as zolpidem tartrate (10 mg/d) for depression and associated anxiety and insomnia.

Six weeks after beginning this treatment regimen and 2 hours after taking her daily dose of bupropion ER, the patient lost consciousness at work and had a grand mal seizure witnessed by her coworkers. She was taken to a local emergency department.

On examination, the patient, a 27-year-old white woman, appeared in good health. Physical and neurologic examination were unremarkable. Complete blood count, serum analysis, and urinalysis laboratory values were normal. She had no premorbid history of epilepsy or neurologic illness, nor any other known predisposing factors to epilepsy. It was determined that she should be kept at the hospital for observation. Buproprion was discontinued, but 8 hours after her first seizure, the patient had a second grand mal seizure, which was observed by emergency department staff. She was started on intravenous phenytoin sodium and was admitted to the hospital for 3 days before being discharged. Results from an electroencephalogram were normal.

Discussion
Bupropion, like other antidepressant agents, lowers seizure threshold. This report is the first published case of seizures induced by bupropion ER. Surprisingly, the patient had seizures even though she was taking two anticonvulsants, including clonazepam, which is considered the most efficacious medication in preventing bupropion-induced seizures.13 That her two seizures occurred 8 hours apart may be accounted for by the properties of the ER formulation. Neither zolpidem nor hydrocodone syrup have seizure listed in prescribing information as a possible adverse event.

The patient remained on clonazepam, lamotrigine, zolpidem, and hydrocodone, seizure-free, for 8 months after this event. No antidepressant was prescribed in place of bupropion. Although bupropion ER offers the convenience of once-daily dosing, the drug’s prolonged half-life may cause seizures to have a more protracted course, as in the case presented. It is recommended that physicians carefully monitor patients taking any form of bupropion.

References