A Case Report of Seizure Induced by Bupropion Nasal Insufflation

Sir: Bupropion hydrochloride (HCl) is an aminoketone antidepressant currently approved by the U.S. Food and Drug Administration (FDA) for depression and smoking cessation. Off-label uses include treatment of attention-deficit/hyperactivity disorder, chronic fatigue, and cocaine dependence and adjunctive treatment for Parkinson's disease. Bupropion is available in 3 formulations: immediate-release (IR), sustained-release (SR), and extended-release (XL).

Bupropion-induced seizures have been described in safety surveillance studies and case reports. As with other antidepressants and psychotropic medications, bupropion appears to lower the seizure threshold in a dose-dependent fashion. The seizure incidence in patients taking ≤ 450 mg per day of bupropion IR is 0.4%, while the incidence in those taking 600 to 900 mg per day is 2.8%.[1,2] This elevated risk of seizure led to a lowering of the maximum dose and the development of sustained- and extended-release products. The seizure rate for the sustained-release formulation decreased to 0.1% at doses of up to 300 mg per day.[2] An emergency medicine study revealed that bupropion was the third leading cause of new-onset seizures at 1.4%, behind cocaine and benzodiazepine withdrawal.[3] Overdose literature indicates that 68% to 77% of bupropion-induced seizures occur within 4 hours of ingestion.[1,4]

While bupropion-induced seizures are well described, data reflecting the consequences of bupropion nasal insufflation are limited. A MEDLINE search using the keywords *bupropion* and *insufflation* only revealed 2 letters reporting bupropion nasal insufflation in 2 adolescents, with 1 case resulting in seizure.[5,6] Neither of the 2 letters hypothesized about the mechanism for seizure production. This is the second reported case describing bupropion nasal insufflation–induced seizure.

Case report. Mr. A, a 50-year-old homeless white man with a history of multiple emergency department (ED) admissions was brought into the ED in March 2005 by paramedics secondary to seizures from a standing position witnessed by 2 bystanders. Each seizure lasted 30 to 60 seconds with a brief postictal period and no incontinence. Bystander descriptions of the seizures were unavailable. During the intake history, Mr. A admitted to the nasal insufflation of bupropion SR tablets, but was unable to quantify the amount. The patient admitted to a history of bupropion nasal insufflation occasionally resulting in seizures over the past 3 years. He denied a long-standing seizure disorder or treatment with anticonvulsants. He claimed that this route of administration gives him a chemical euphoria, which he described as a "cocaine high." He did not complain of any auditory or visual hallucinations and exhibited no signs of intoxication.

Mr. A's medical history was significant for substance abuse, questionable schizoaffective disorder, and prior seizures secondary to bupropion nasal insufflation. He denied a family history of seizure disorder or substance abuse. The patient admitted to smoking, but denied any current alcohol or illicit drug use. The patient reported being incarcerated 3 years ago. He reported no medication allergies and that he was prescribed bupropion SR 150 mg orally twice daily and olanzapine 10 mg orally daily. He stated that he receives his medications from various free clinics and EDs in San Diego, Calif. The patient denied the use of any over-the-counter or herbal medications. He was deemed a reliable historian based on his alertness and ability to provide a thorough intake history.

Upon presentation to the ED, Mr. A was stable, alert, and oriented. Results of the physical examination were normal except for a small hematoma and abrasion over the right eye, with no focal neurologic deficits. Tachycardia with a heart rate of 112 was noted, but results of the cardiac examination were otherwise normal. The complete blood count and metabolic panel were within normal limits. His blood alcohol level was negative. A urine toxicology screen was collected but not completed. Previous urine toxicology screens over the past 6 months were negative. A plasma bupropion level was not evaluated during this admission. Brain computed tomography scan results were nonsignificant. The ED treatment course consisted of lorazepam 2 mg intravenously and observation for approximately 6 hours. Mr. A displayed no further seizure activity or mental status changes and was deemed stable and safe for discharge. He was counseled to avoid future nasal insufflation of bupropion SR tablets and to follow up with outpatient psychiatric services.

Bupropion HCl is structurally similar to phenylethylamines, which include such compounds as methamphetamine, amphetamine, methylenedioxy-methamphetamine (MDMA, "Ecstasy"), and diethylpropion.[7] In addition, the 3-dimensional structure of bupropion resembles that of cocaine. Bupropion is a weak catecholamine reuptake inhibitor that affects predominantly dopamine, norepinephrine, and serotonin.[8,9] While the exact mechanism of action is unclear, animal studies suggest that bupropion enhances dopaminergic and noradrenergic activity.[8,9]

The stimulant effects of bupropion have been studied because it has structural similarities to amphetamine and there is evidence indicating that bupropion produces stimulant effects in animals.[10] A study by Griffith et al.[11] compared oral bupropion with oral amphetamine to determine its abuse potential. The physiologic effects of oral bupropion were not significantly different than placebo for all subjective and objective measures testing stimulant effects. The authors concluded that the pharmacologic profile of oral bupropion was not similar to that produced by amphetamine. They also concluded that it is unlikely for oral bupropion to produce amphetamine-like abuse patterns. Despite limited information, the increasing illicit use of intranasal bupropion, gabapentin, quetiapine, trihexyphenidyl, and tricyclic antidepressants has been recognized in prison populations (Del Paggio[12] and Deborah Lomeli, Pharm.D.; Atascadero State Hospital, Atascadero, Calif.; personal communication, August 2005). Information disseminated on the Internet suggests that this practice may be growing among individuals experimenting with illicit drugs and other psychotropics.[13]

For intranasal bupropion to result in seizures, significantly elevated levels of bupropion in the body would be required. While no data are available to determine the rate and extent of nasal absorption of bupropion, it is known that various drugs are efficacious after intranasal administration, including cocaine, epinephrine, fentanyl, and methamphetamine. The absorption of these drugs is dependent on their physical and chemical properties. The nasopharynx

has a large, highly vascularized surface area for drug absorption. Drug entry occurs through systemic absorption from nasal mucosa, direct entry into the brain, and/or neuronal transport along the olfactory bulb.[14] Since bupropion is a small, lipophilic drug that is readily and extensively absorbed into the body,[15,16] it is likely that systemic absorption will occur after nasal insufflation. Since bupropion is structurally similar to methamphetamine, the deposition of intranasal bupropion may be similar to that of intranasal methamphetamine. The route of administration can dramatically affect the amount of drug present in the body. One study found the intranasal bioavailability of methamphetamine to be 79% and the oral bioavailability to be 67%.[17,18] This 12% increase in bioavailability into the systemic circulation may explain why the onset of action is faster and peak effects are more pronounced with insufflation. The oral bioavailability of bupropion is approximately 5%,[19] and consequently it is reasonable that an increase in bioavailability will occur after intranasal administration. Even a modest increase in bioavailability would result in a significant elevation of peak concentrations and a shortened time of onset than with oral administration.

The pharmacokinetics of bupropion have only been described after oral administration, but the alteration in bupropion disposition after nasal insufflation can be predicted based on the knowledge that bupropion is a high-extraction, hepatically eliminated drug. The venous equilibrium model describing hepatic clearance dictates that the clearance of bupropion is a perfusion rate-limited elimination, meaning that bupropion is cleared from the blood as quickly as it is delivered to the liver. Since the intrinsic clearance of bupropion is dependent on hepatic blood flow, assuming this is not changing significantly, a decrease in the effective extraction ratio after nasal insufflation would explain elevated drug levels. The extraction ratio is the percent decrease in the concentration of the drug as it is removed from the blood by the liver. After oral administration, the entire dose of bupropion would be directly delivered to the liver from the gastrointestinal tract with approximately 95% of the dose being metabolized, primarily by cytochrome P450 2B6, before being distributed throughout the rest of the body. With nasal insufflation, the bupropion dose would be delivered to the entire body before circulating through the liver, leaving a higher proportion of intact drug, resulting in an elevated peak plasma concentration (C_{max}) and increased area under the curve (AUC).

A single-dose pharmacokinetic study revealed that bupropion IR had a C_{max} of approximately 190 ng/mL, twice that of bupropion SR at 90 ng/mL, and that the AUC and half-life were similar for both formulations.[2] While the therapeutic range of bupropion has not been confirmed, pharmacokinetic studies suggest that the trough range may be between 10 to 100 ng/mL.[20–22] In a case series evaluating plasma bupropion levels in patients who developed seizures, the mean plasma level 6 hours postseizure was 170 ng/mL.[23] Although safety surveillance and toxicology studies suggest that elevated and rapidly increasing plasma bupropion levels increase the risk of seizure, plasma levels have not correlated well with either the therapeutic effect or the incidence of seizures.[21–23] After nasal insufflation, plasma bupropion levels may increase faster and be higher than those seen with oral administration of bupropion IR and could explain the production of seizures.

While there are several factors that support production of seizures by bupropion nasal insufflation, there are limitations within this case. The patient claimed to be prescribed and properly taking olanzapine concurrently, which could reduce the seizure threshold. The incidence of seizures with olanzapine is 0.9%. Moreover, the patient had a history of alcohol abuse, which could increase his risk of seizures. On physical examination, a slight tachycardia was present, which is a common sign in bupropion overdose or mild alcohol withdrawal. Another limitation is that a toxicology screen was not completed to rule out any illicit drug use. Also, the patient could not state the number of tablets insufflated. Finally, since serum bupropion levels have not correlated well with therapeutic effects or toxicity, a bupropion drug level was not obtained to help confirm bupropion intoxication.

Bupropion is FDA-approved for the treatment of depression and nicotine dependence. The incidence of seizure with orally administered bupropion has been described in safety surveillance and toxicology literature. However, there is a paucity of literature discussing the role of bupropion nasal insufflation in the production of seizures. This case describes a patient who developed seizures after the nasal insufflation of bupropion SR tablets.

The authors report no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Johnston JA, Lineberry CG, Ascher JA, et al. A 102-center prospective study of seizure in association with bupropion. J Clin Psychiatry 1991;52:450–456
2. Dunner DL, Zisook S, Billow AA, et al. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. J Clin Psychiatry 1998;59:366–373
3. Pesola GR, Avasarala J. Bupropion seizure proportion among new-onset generalized seizures and drug related seizures presenting to an emergency department. J Emerg Med 2002;22:235–239
4. Shepherd G, Velez LI, Keyes DC. Intentional bupropion overdoses. J Emerg Med 2004;27:147–151
5. Welsh CJ, Doyon S. Seizure induced by insufflation of bupropion [letter]. N Engl J Med 2002;347:951
6. Khurshid KA, Decker DH. Bupropion insufflation in a teenager. J Child Adolesc Psychopharmacol 2004;14:157–158
7. Mehta NB. The chemistry of bupropion. J Clin Psychiatry 1983;44:56–59
8. Preskorn SH, Othmer SC. Evaluation of bupropion hydrochloride: the first of a new class of atypical antidepressants. Pharmacotherapy 1984;4:20–34
9. Ferris RM, White HL, Cooper BR, et al. Some neurochemical properties of a new antidepressant, bupropion hydrochloride (Wellbutrin). Drug Develop Res 1981;1:21–35
10. Cooper BR, Hester TJ, Maxwell RA. Behavioral and biochemical effects of the antidepressant bupropion: evidence for selective blockade of dopamine uptake in vivo. J Pharmacol Exp Ther 1980;215:127–134
11. Griffith JD, Carranza J, Griffith C, et al. Bupropion: clinical assay for amphetamine-like abuse potential. J Clin Psychiatry 1983;44:206–208
12. Del Paggio D. Psychotropic medication abuse in correctional facilities. Bay Area Psychopharmacol Newsletter 2005;8:1–5
13. Erowid. Erowid experience vaults: bupropion. Available at: http://www.erowid.org/experiences/subs/exp_Pharms_-_Bupropion.shtml. Accessed Oct 3, 2005
14. Graff CL, Pollack GM. Nasal drug administration: potential for targeted central nervous system delivery. J Pharm Sci 2005;94:1187–1195
15. Schroeder DH. Metabolism and kinetics of bupropion. J Clin Psychiatry 1983;44:79–81
16. Lai AA, Schroeder DH. Clinical pharmacokinetics of bupropion: a review. J Clin Psychiatry 1983;44:82–84
17. Harris DS, Boxenbaum H, Everhart ET, et al. The bioavailability of intranasal and smoked methamphetamine. Clin Pharmacol Ther 2003;74:475–486
18. Cook CE, Jeffcoat AR, Hill JM, et al. Pharmacokinetics of

methamphetamine self-administered to human subjects by smoking S-(+)-methamphetamine hydrochloride. Drug Metab Dispos 1993;21:717–723
19. Butz RF, Schroeder DH, Welch RM, et al. Radioimmunoassay and pharmacokinetic profile of bupropion in the dog. J Pharmacol Exp Ther 1981;217:602–610
20. Goodnick PJ. Pharmacokinetics of second-generation antidepressants: bupropion. Psychopharmacol Bull 1991;27:513–519
21. Preskorn SH. Antidepressant response and plasma concentrations of bupropion. J Clin Psychiatry 1983;44:137–139
22. Davidson J. Seizures and bupropion: a review. J Clin Psychiatry 1989;50:256–261
23. Goodnick PJ. Blood levels and acute response to bupropion. Am J Psychiatry 1992;149:399–400

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Treatment of Temporomandibular Pain With the Selective Serotonin Reuptake Inhibitor Paroxetine

Sir: In clinical dentistry, patients frequently have orofacial pain caused by temporomandibular disorder (TMD). TMD is characterized by a combination of symptoms affecting the temporomandibular joint and/or chewing muscles. Patients with TMD usually develop chronic or recurrent pain, contracture/tenderness of chewing muscles, clicking condylar noise, limitation of jaw function, and limited mouth opening.

In the treatment of TMD, various types of dental therapy, such as occlusal splints and physical therapy, are used. Chronic TMD pain is usually treated with analgesics and muscle relaxants. However, these drugs do not always contribute to the success of treatment. Recently, the use of tricyclic antidepressants (TCAs) has been proposed, and the agents have demonstrated efficacy in controlling chronic pain.[1] Furthermore, a possible role of the new selective serotonin reuptake inhibitor antidepressants (SSRIs) has been proposed for chronic pain management with better tolerability by reducing the incidence of side effects, leading to higher patient compliance when compared with TCAs.[2]

We report 2 patients with chronic pain due to long-term TMD in whom chronic pain was markedly reduced following administration of the SSRI paroxetine hydrochloride. We obtained informed consent from these patients for this report.

Case 1. Ms. A, a 64-year-old woman, developed tinnitus, ear pain, shoulder stiffness, and insomnia, for which a psychiatry clinic prescribed a minor tranquilizer and hypnotics at the age of 52 years. At the age of 61 years, she developed limitation of mouth opening, pain in the temporomandibular region, and tongue pain. She consulted a dental clinic. Pain was extended to both sides in her mouth, and splint therapy and mouth opening training were administered. The pain gradually worsened and fluctuated due to mental stress. She was referred to our psychiatric department.

As to her odontological diagnosis, masticatory muscle disturbance was doubted because of persistent bruxism. She complained of pain on both sides of the temporomandibular articulation as well as the tongue. Anxieties regarding her husband's health and uneasiness about the future were considered background mental factors. She scored 44 points on a self-rating depression scale (SDS).[3] She was diagnosed with DSM-IV pain disorder. Administration of paroxetine 10–20 mg/day reduced muscle tension and pain in the lower jaw in about 3 weeks. The intensity of pain and discomfort was evaluated using a visual analog scale (VAS) and distance of opening mouth. The mouth-opening movements were registered by the distance between incisal edges. At rest, her mouth opening improved from 27 mm to 38 mm, and her VAS score decreased from 100 mm to 30 mm.

Case 2. Ms. B, a 24-year-old woman, developed a sense of discomfort that was disabling and pain in the temporomandibular region on yawning around the age of 20 years. She was able to open her mouth less each day. At the age of 22 years, she consulted a dental clinic (different from the clinic in case 1). Ms. B's mouth opening was improved by splint treatment from 8 mm to 25 mm, and her pain almost disappeared. At the age of 24 years, the pain began again. She was referred to our psychiatric department with comorbid mental uneasiness.

She complained of anxiety over worsening of TMD and her future. Her SDS score was 48 points. She was diagnosed with DSM-IV pain disorder. Administration of paroxetine 10–20 mg/day reduced tension and pain of the jaw in about 2 weeks. The distance of her mouth opening improved from 19 mm to 26 mm, and her VAS score decreased from 100 mm to 30 mm.

TMD patients may have symptoms that are acute and resolve without therapy or with only limited, conservative therapy. For chronic TMD, drug therapy with analgesics is usually indicated. However, in some cases, analgesics are ineffective. Antidepressants have an antinociceptive (analgesic) effect on chronic pain independent of the antidepressant effect.[4] In the past, TCAs were considered the gold standard in the treatment of different kinds of neuropathic pain, as studies showed their superiority compared to placebo or other available drugs.[2] There have been case studies[1,5] demonstrating that TCAs were sufficient to significantly reduce pain and discomfort due to chronic TMD. However, with TCA treatment, a large number of side effects are observed, which, although not life-threatening, significantly affect the patient's quality of life, causing a limitation of tolerability. Common side effects include dry mouth, sedation, memory impairment, constipation, and orthostatic hypotension. Patients who are intolerant or resistant to TCAs may be treated with SSRIs.[6] Although a complex mechanism underlies the antinociceptive effects of antidepressants, it is suggested that SSRI-induced antinociception involves both central opioid and serotonergic pathways.[7]

Until now, there have been no case reports describing the beneficial effects of SSRIs for TMD patients. We report 2 patients with chronic or recurrent pain due to long-term TMD who were treated with an SSRI. These patients were diagnosed with TMD and received standard dental therapy along with analgesics without significant efficacy. Administration of the SSRI paroxetine remarkably reduced the persistent and unpleasant pain of TMD within a short period without side effects.

SSRIs can be beneficial in reducing TMD pain complaints as one method of dental therapy. Dentists and physicians, including psychiatrists, should have an understanding of the increasing utilization of SSRIs for managing chronic TMD pain.

TMD develops from multiple factors, causing long-term pain and interfering with the patient's daily life. The biopsychosocial conceptualization of the pain experience illustrates the close connection between pain and psychosocial factors. Common emotional problems include anxiety, depression, and anger. It is important to recognize and treat psychiatric or emotional concerns as well as physical symptoms.[8]

Although dental treatment should be a priority in cases of TMD when psychiatric factors dominate, a psychosocial approach is also needed.

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REFERENCES

1. Rizzatti-Barbosa CM, Nogueira MTP, de Andrade ED, et al. Clinical evaluation of amitriptyline for the control of chronic pain caused by temporomandibular joint disorders. Cranio 2003;21:221–225
2. Mattia C, Paoletti F, Coluzzi F, et al. New antidepressants in the treatment of neuropathic pain: a review. Minerva Anestesiol 2002;68: 105–114
3. Zung WWK. A self-rating depression scale. Arch Gen Psychiatry 1965;12:63–70
4. Fishbain D. Evidence-based data on pain relief with antidepressants. Ann Med 2000;32:305–316
5. Pettengill CA, Reisner-Keller L. The use of tricyclic antidepressants for the control of chronic orofacial pain. Cranio 1997;15:53–56
6. Aragona M, Bancheri L, Perinelli D, et al. Randomized double-blind comparison of serotonergic (Citalopram) versus noradrenergic (Reboxetine) reuptake inhibitors in outpatients with somatoform, DSM-IV–TR pain disorder. Eur J Pain 2005;9:33–38
7. Singh VP, Jain NK, Kulkarni SK. On the antinociceptive effect of fluoxetine, a selective serotonin reuptake inhibitor. Brain Res 2001; 915:218–226
8. Gremllion HA, Waxenberg LB, Myers CD, et al. Psychological considerations in the diagnosis and management of temporomandibular disorders and orofacial pain. Gen Dent 2003;51:168–172

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Alleviation of Hot Flashes With Increase in Venlafaxine Dose

Sir: Venlafaxine, a newer bicyclic antidepressant, acts as a serotonin-norepinephrine reuptake inhibitor (SNRI). Besides improving depressive symptoms, venlafaxine has also been demonstrated to alleviate vasomotor symptoms.[1] It is being increasingly used as a nonhormonal drug to treat hot flashes, mostly in those women with concerns about or contraindications to estrogen-containing preparations.[2] We report an interesting case of new onset of hot flashes in a postmenopausal woman who was being treated with venlafaxine for chronic depression. The symptoms of hot flashes were alleviated with increase in the dose of venlafaxine and reemerged with decrease in the dose.

Case report. Ms. A is a 54-year-old woman with a long-standing history of schizoaffective disorder, which required more than 10 hospitalizations over the past 20 years. Her psychosis was under good control with aripiprazole, and she had been free of hallucinations and delusions. She had a history of 2 suicide attempts in the remote past. She reported occasional depression, which was well controlled with a small dose of venlafaxine, 75 mg daily, that she had been taking for over a year. No alcohol or drug use has been reported in the last 20 years. Her medical history included seizure disorder, which was well controlled with phenytoin. She had been free of seizure episodes for a year. Other medical illnesses include type 2 diabetes, hypercholesterolemia, gastroesophageal reflux disorder, hypertension, and urinary incontinence. Her medications included venlafaxine 75 mg daily, aripiprazole 30 mg daily, lamotrigine 200 mg twice daily, metoprolol 12.5 mg twice daily, rosiglitazone 4 mg daily, simvastatin 40 mg at bedtime, phenytoin 300 mg at bedtime, and temazepam 15 mg as needed for insomnia.

She complained of new-onset hot flashes at a frequency of 8 to 10 episodes a day over the last 3 months. Each episode lasted for 20 minutes with intense feeling of flushing initially followed by intense feeling of cold. Venlafaxine was increased to 150 mg daily, as a previous report[3] has shown benefits of venlafaxine in treatment of hot flashes. With the increase in the dose of venlafaxine, the patient reported reduction in hot flashes both in frequency and severity. The hot flashes decreased in frequency to 2 episodes per day with each episode lasting for only 5 to 10 minutes.

Within a week of increasing the dose of venlafaxine, she reported worsening of the tremor in her hands. She also stated that the jerky movements in her extremities increased. We attributed her increased tremulousness and jerkiness to enhanced noradrenergic stimulation from the increased dose of venlafaxine; hence, we decreased the dose of venlafaxine to 75 mg daily. She reported decrease in tremors but an increase in the frequency of hot flashes after 7 days of reducing the dose of venlafaxine. We increased the dose of venlafaxine to 150 mg again, which resulted in a prompt control of hot flashes within a week. We consulted a neurologist for the management of tremulousness.

In addition to its well-established efficacy in treatment of depression, venlafaxine has also been found to be effective in decreasing the number and frequency of hot flashes.[4] Although estrogen has been used for many years for treating hot flashes, concern about its safety has precluded its use largely due to the findings of the Women's Health Initiative trial.[2] Newer antidepressants are being investigated as an alternative means for alleviating hot flashes.[5] Venlafaxine is one of the newer antidepressants that has also been used as a nonhormonal treatment for hot flashes in cancer survivors[4] and in postmenopausal women.[3] A beneficial effect on vasomotor symptoms with the use of venlafaxine has also been reported in perimenopausal women with depression.[1]

In the present case, we observed reappearance of hot flashes in a postmenopausal woman who was being treated with venlafaxine 75 mg daily for a year for depression. Interestingly, increasing the dose of venlafaxine to 150 mg daily alleviated her hot flashes. The exact mechanism of venlafaxine to alleviate hot flashes remains unknown. Venlafaxine is known to affect both serotonin as well as norepinephrine reuptake. Effects of venlafaxine at lower doses are thought to be related to the serotonin reuptake inhibition, and at higher doses its effects are attributed to a combination of both serotonergic and noradrenergic effects.[6]

The physiologic mechanism underlying hot flashes is not completely known. Two hypotheses have been proposed for the mechanism of hot flashes.[3] According to one theory, changes in estrogen levels at menopause alter central nervous system adrenergic neurotransmission and cause abnormal thermoregulation. Another hypothesis is that decreased estrogen levels at menopause lowers serotonin levels, and the changes in serotonergic neurotransmission might cause hot flashes. In the present case,

the new onset of hot flashes while being treated with a lower dose of venlafaxine is probably related to its effect on serotonin reuptake inhibition. The alleviation of hot flashes at a higher dose may involve its action on both serotonergic and noradrenergic pathways or on a predominantly adrenergic pathway.

A possibility of drug-drug interaction should also be noted in this report, as the patient was taking phenytoin. Phenytoin is a potent cytochrome P450 3A4 inducer and can decrease the levels and effects of venlafaxine. However, the patient had been on the same dose of both phenytoin and venlafaxine over the last year. Therefore, in the present case, the new onset of hot flashes cannot be explained by the drug interaction. No other drug-drug interactions were found regarding venlafaxine.

In conclusion, although venlafaxine has shown success as a treatment for hot flashes in postmenopausal women, this response could be dose related.

The authors report no financial affiliations or other relationships relevant to the subject of this letter.

REFERENCES

1. Ladd CO, Newport DJ, Ragan KA, et al. Venlafaxine in the treatment of depressive and vasomotor symptoms in women with perimenopausal depression. Depress Anxiety 2005;22:94–97
2. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy menopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–333
3. Evans ML, Pritts E, Vittinghoff E, et al. Management of postmenopausal hot flushes with venlafaxine hydrochloride: a randomized, controlled trial. Obstet Gynecol 2005;105:161–166
4. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059–2063
5. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA 2006;295:2057–2071
6. Debonnel G, Saint-Andre E, Hebert C, et al. Differential physiological effects of a low dose and high doses of venlafaxine in major depression. Int J Neuropsychopharmacol 2006 May 11:1–11 [Epub ahead of print]

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Psychosis Precipitated by Acetyl-L-Carnitine in a Patient With Bipolar Disorder

Sir: Alternative and complementary medicine is popular in the United States, and interest in this type of medicine is growing. Approximately 55% of the U.S. population uses complementary and alternative medicines, at a cost of $337 million in 2001.[1] Knaudt et al.[2] found that 54% of outpatients with psychiatric conditions used alternative medicines in addition to conventional medicines to treat psychiatric symptoms.

Acetyl-L-carnitine (ALC) is a popular nutritional supplement used by patients with mood disorders, Alzheimer's disease, and other disorders. It is widely sold over the Internet as a safe and effective nutritional supplement. There is also a general perception among the public that nutritional supplements are safe, with few side effects. To our knowledge, there are no reports of ALC precipitating a psychiatric disorder. We report the first case of ALC precipitating a psychotic episode in a person with a previous history of bipolar disorder.

Case report. Mr. A, a 52-year-old white man, admitted as an inpatient to our psychiatric unit in 2005 after he became floridly psychotic. He presented with auditory hallucinations of the devil and persecutory delusions regarding his brother and mother, who were his primary caregivers. On admission, he demonstrated hostility and aggression toward the staff in the unit. He also was verbally threatening and physically assaultive toward staff.

Mr. A had a long history of bipolar disorder dating back to early adulthood. He had been stabilized on lithium treatment and had been symptom free for more than 10 years. His symptoms had reemerged about 2 years ago, and, prior to the current admission, the patient had been admitted 3 months ago for inappropriate sexual behaviors, which had been treated successfully with citalopram. He had been discharged on a treatment regimen of lithium, 150 mg b.i.d., and citalopram, 20 mg/day, and had been off treatment with antipsychotics for more than 3 months before the current admission (he had received aripiprazole, olanzapine, clozapine, and quetiapine in the past). His condition was stable, and he had been doing very well for 4 weeks. Five days before admission, the patient was started on treatment with nutritional supplements including vitamin C, vitamin E, and ALC, the latter at 500 mg/day. Five days after ALC was started, the patient suddenly became psychotic.

We believe that ALC was responsible for the precipitation of this current psychotic episode because of the temporal association of the onset of psychosis with the start of ALC treatment, the suddenness of the onset, and the severity of the psychosis, which was much greater than he had experienced in a long time.

ALC is a well-known nonessential organic nutrient. Because ALC is essential for the transport of long-chain fatty acids across the inner mitochondrial membrane, it has major importance in mitochondrial energy metabolism. ALC is easily transported across the blood-brain barrier and improves neuronal and repair mechanisms while modifying acetylcholine production in the central nervous system.[3]

Esters of carnitine (acetylcarnitine and propionylcarnitine) have pharmacologic value by virtue of their antioxidant properties and ability to deliver readily oxidizable carbon units to mitochondria. Alzheimer's disease and depression in the elderly, ischemia-induced myocardial dysfunction in angina pectoris, human immunodeficiency virus infection, and diabetic neuropathies may respond positively to ALC administration.

Animal studies have shown that ALC administration persistently increases dopamine outflow in the nucleus accumbens.[4] Carnitine supplementation has been shown to significantly increase the levels of dopamine in the cortex, hippocampus, and striatum of rat brain.[3]

Dopamine dysregulation in this pathway has been shown to cause psychotic symptoms. This dysregulation may arise through a process of sensitization, which, in animals, can be caused by repeated administration of dopamine-releasing drugs. The same process may occur in humans, and some indi-

viduals may be particularly sensitive to the effects of such drugs either for genetic reasons or through early environmental damage.[5]

This case report illustrates the need for physicians to be aware of any complementary therapies that patients might be receiving and to routinely inquire about this during the initial interview. Psychiatrists need to be aware of the potential that these therapies have to exacerbate or worsen preexisting psychiatric disorders.

Drs. Evcimen, Mania, Mathews, and Basil report no financial affiliation or other relationship relevant to the subject of this letter.

REFERENCES

1. Blumenthal M. Herb sales down in mainstream market, up in natural food stores. HerbalGram Summer 2002;No. 55:60
2. Knaudt PR, Connor KM, Weisler RH, et al. Alternative therapy use by psychiatric outpatients. J Nerv Ment Dis 1999;187:692–695
3. Juliet PA, Balasubramaniam D, Balasubramaniam N, et al. Carnitine: a neuromodulator in aged rats. J Gerontol A Biol Sci Med Sci 2003;58:970–974
4. Scheggi S, Rauggi R, Nanni G, et al. Repeated acetyl-l-carnitine administration increases phospho-Thr34 DARPP-32 levels and antagonizes cocaine-induced increase in Cdk5 and phospho-Thr75 DARPP-32 levels in rat striatum. Eur J Neurosci 2004;19:1609–1620
5. Howes OD, McDonald C, Cannon M, et al. Pathways to schizophrenia: the impact of environmental factors. Int J Neuropsychopharmacol 2004;7(suppl 1):S7–S13

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