of an optimistic review with respect to lithium.

Lithium and valproate were both valuable in improving manic symptoms, but lithium illustrated more efficacious incidentally.

AUTHOR DISCLOSURE INFORMATION

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Possible Varenicline-Induced Paranoia and Irritability in a Patient With Major Depressive Disorder, Borderline Personality Disorder, and Methamphetamine Abuse in Remission

To the Editors:

Varenicline was introduced into the market in 2006 for smoking cessation. In November 2007, the Food and Drug Administration announced that it had received postmarketing reports that patients using varenicline for smoking cessation had experienced several adverse psychiatric events, including suicidal ideation and erratic behavior. There are 3 case reports in the literature of exacerbated psychotic or hypomanic symptoms in 3 patients with schizophrenia or bipolar disorder, but no other case reports in any other psychiatric patients have been reported to my knowledge. I report here the case of a patient who received varenicline twice and became quite paranoid on both occasions.

CASE REPORT

A 35-year-old woman with major depressive disorder (in partial remission), generalized anxiety disorder, borderline personality disorder (currently stable), and crystal methamphetamine abuse (now in full remission) was being treated with weekly therapy and a medication regimen (with no changes for 2 months) of topiramate 200 mg PO daily, duloxetine 120 mg PO daily, modafinil 400 mg PO daily, and clonazepam 2 mg PO at night. She had been abstinent from crystal methamphetamine for 6 months, as confirmed by monthly random urine toxicology screening. She smoked approximately 1 pack per day of cigarettes, and also smoked 1 joint of marijuana daily, but otherwise she had no other drug use. She wanted to stop smoking and was prescribed varenicline according to the manufacturer’s instructions, to a final dose of 1 mg PO BID. While taking the varenicline, she became increasingly paranoid, believing that people were talking about her and looking at her on the street and at work. This was very similar to paranoia that she had experienced 1 year prior while abusing crystal methamphetamine, but she convincingly denied current methamphetamine abuse, which was confirmed by negative urine toxicology screens over a 1-month period, and she also denied any change in the quantity or quality of the marijuana that she smoked. The varenicline was stopped, and the paranoia resolved gradually over 2 weeks. The patient had found varenicline to be very helpful for smoking cessation, so it was decided to retry this medication at a lower dose. However, at 0.5 mg PO BID, she again became quite paranoid, thinking that people several rows back in an airplane were talking about her, and she also became much more irritable, so much so that she had an altercation at her workplace and was subsequently fired. Varenicline was again stopped, with resolution of the paranoia and decreased irritability. Since the discontinuation of varenicline (approximately 6 months ago), this paranoia has not recurred, and she has remained abstinent from crystal methamphetamine for more than 1 year now. Unfortunately, she has begun smoking cigarettes again, but now to a lesser extent.

DISCUSSION

Nicotine is known to activate several classes of brain cholinergic receptors, including many high-affinity receptors composed primarily of α4 and β2 subunits. These receptors are presynaptic, and their activation leads to the release of dopamine and other neurotransmitters, accounting for the pleasurable effects of smoking. Varenicline is principally a partial agonist at the α4-β2 nicotinic acetylcholine receptor, activating the receptor to cause release of dopamine at a low level while also blocking nicotine binding. During abstinence from cigarette smoking, this can lead to more sustained release of dopamine in comparison to the briefer pulses of dopamine with each cigarette smoked. It is possible that the increased psychoses in this susceptible patient was triggered by this elevated and sustained level of dopamine release. Of course, given her complicated history and requirement for several concomitant medications, it is not possible to conclude with certainty that the paranoia was directly related to the varenicline use. However, it is notable
that the patient did not alter her medication regimen or illicit drug use in any way, other than starting varenicline. In addition, the paranoia temporarily coincided with varenicline use and recurred again with varenicline rechallenge.

The above case highlights further concerns with possible neuropsychiatric side effects associated with varenicline use in patients with psychiatric issues. Further safety assessment in this patient population will be needed, and physicians should consider and monitor for possible psychiatric side effects when prescribing this medication to patients with preexisting psychiatric disorders or vulnerability to psychoses.

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**Five Female Cases of Prolonged Depression in Chronic Anorexia Nervosa Treated With Selective Estrogen Receptor Modulator Raloxifene-Augmented Therapy**

To the Editors:

Depression that reaches levels requiring clinical attention can frequently be observed in female patients with anorexia nervosa (AN). 1-3 The lifetime prevalence of major depression for females with AN ranges from 20% to 80% and dysthymia from 19% to 93%. 4, 5 Anorexia nervosa patients presenting with depression may not necessarily show ordinary, typical depressive mood characteristics. In addition to a depressive mood and inability, these patients occasionally have a poor interoceptive awareness to identify their own mood states, resulting in the so-called alexithymia. Frustration and social isolation marked by chronic disorders, as well as the psychopathology of AN, which includes low self-esteem and body image disturbances, exert a further influence on the patients’ mood. Malnutrition, a secondary condition of anorexia, along with metabolic and endocrine disorders, is reported to influence the mood status of the patients. 5-7 Until recently, several antidepressants have been used for treating AN not only to improve obsessive symptoms in relation to the patient’s abnormal eating behavior but also to treat depression. However, placebo-controlled studies on conventional antidepressants for AN show disappointing results in terms of efficacy. 8-10

Selective estrogen receptor modulators (SERMs), like raloxifene, function as agonists for estrogen receptors of the skeletal system, central nervous system (CNS), and the cardiovascular system and function as antagonists for mammary glands and the female reproductive system. 11, 12 These pharmacological characteristics make SERMs generally suitable to be prescribed for treating osteoporosis in postmenopausal women. Recently, there have also been reports of SERMs being used as an antidepressant augmentation. 13, 14 This function is possibly caused by the stimulation of estrogen receptors in the CNS. 14, 15

We used raloxifene for treating persistent depression in female patients with chronic AN who had a resistance to antidepressants and present 5 cases where an improvement in depression was observed. This project was approved by the medical ethical committee of the Faculty of Medicine at Shinshu University, and we obtained an informed consent from all participants before the study. All 5 patients out of 5 entries were diagnosed with AN based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and as described in Table 1. All patients were females who had AN for more than 10 years, as well as bouts of prolonged depression, and had a history of more than 3 failed pharmacotherapies for depression. The average age of these women was 39.6 years (SD, 9.4 years), and the average duration of their disorder was 18.8 years (SD, 6.1 years). The average body mass index of the patients at the start of therapy was 13.5 kg/m2 (SD, 0.5 kg/m2), which was about 60% of their medically recommended body weight. In regard to these patients’ depression, the precise duration of their depressive symptoms was unclear but continued for at least a minimum of 5 years. Pharmacotherapy using antidepressants continued for more than 3 years, which was not observed to be effective. No change in the pharmacotherapy for each patient occurred, in a minimum, the 6 months before starting this treatment intervention.

A continual dosage of 60 mg/d of raloxifene (average, 1.75 mg/kg per day; SD, 0.21 mg/kg per day) was administered to each patient. The extent of the patients’ depression was assessed using the 21-item version of Hamilton Depression Rating Scale (HDRS), 16 which returned to an average baseline of 33.8 (SD, 3.0). Four weeks after commencing raloxifene administration, the average score reduced to 29.8 (SD, 5.1); no significant difference was observed relative to the levels before beginning the treatment (P = 0.2980). However, 8 weeks after commencing administration, the average HDRS score was 19.8 (SD, 1.6); a significant decrease was observed relative to both the score before treatment (P = 0.0001) and the score obtained at 4 weeks (P = 0.0023). Score analysis showed that improvement occurred primarily in symptoms associated with mood and anxiety, whereas almost no change was observed in physical symptoms. Furthermore, psychological symptoms of AN other than depression showed almost no change throughout the course of treatment. We also ensured that, through the duration of this study, there was no change in pharmacotherapy other than raloxifene, including antidepressants and vitamin supplements, or strategies of psychotherapy.

In the HDRS scores, 3 items (assigned 6 points) are related to the unavoidable general physical symptoms, gastrointestinal symptoms, and decreased libido. No change in these symptoms was