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Parkinsonism and Rabbit Syndrome After Discontinuation of Low-Dose Ziprasidone and Concomitant Initiation of Sertraline

To the Editors:

Ziprasidone is an atypical antipsychotic that is chemically unlike any other current antipsychotic medication, has a high 5-hydroxytryptamine 2A (HT_{2A})/D_2 receptor affinity ratio, and has a low liability for extrapyramidal symptoms (EPS).[1] Recent studies have suggested that ziprasidone dosages greater than 120 mg/d may be needed to attain sufficient D_2 receptor occupancy for antipsychotic effects.[2,3] As patients are prescribed higher ziprasidone doses, it remains to be seen if there will be an increased incidence of ziprasidone-induced EPS. Indeed, there have been reports of acute dystonia,[4] parkinsonism,[5] oculogyric crisis,[6] tardive dyskinesia (TD),[7,8] and withdrawal akathisia[9] associated with ziprasidone. In contrast, this is an intriguing case of parkinsonism and rabbit syndrome after the abrupt discontinuation of *low-dose* ziprasidone and concomitant initiation of sertraline.

CASE REPORT

A 58-year-old white woman with a diagnosis of bipolar disorder has had 2 remote manic episodes and recurrent, often treatment-refractory depression. She had past medication trials of aripiprazole and lamotrigine, which were both discontinued because of ineffectiveness against past depression, and quetiapine, which was discontinued because of weight gain. For the past 9 months, she was maintained on ziprasidone 40 mg twice a day, although she was not taking these doses with food. However, for the past month, she had worsening depression and agreed to a course of electroconvulsive therapy, which led to remission of her depression 2 years prior. Two days before her scheduled admission, her ziprasidone was abruptly discontinued, and she was started on sertraline 50 mg daily, which had reportedly been efficacious years earlier. On admission, she was found to have new-onset mild bradykinesia, masked facies, shuffling gait, and a high-amplitude tremor of her right leg without subjective restlessness. In addition, she had prominent high-frequency chewing movements with occasional lip puckering, without obvious tongue involvement and which she could not voluntarily suppress. No choreoathetoid or other involuntary movements were noted. Her sertraline was discontinued, and she was given immediate doses of benztropine 2 mg and ziprasidone 60 mg followed by ziprasidone 40 mg twice a day. Symptoms of her parkinsonism and orofacial dyskinesia reportedly improved within hours and were completely resolved within 18 hours. Her ziprasidone was tapered over the course of 3 days with no reemergence of EPS. She was subsequently discharged on lithium, which she had reportedly never taken, to be titrated and monitored by her outpatient psychiatrist.

DISCUSSION

This is the first case report of parkinsonism and orofacial dyskinesias as a possible effect of the discontinuation of ziprasidone and initiation of sertraline. In the case presented, the orofacial dyskinesias are consistent with a diagnosis of rabbit syndrome, a rare form of EPS characterized by involuntary 5-Hz, rhythmic, vertical movements of the mouth and lips without involvement of the tongue.[10] Unlike TD and other types of oral dyskinesias, rabbit syndrome cannot be voluntarily suppressed by the patient.[11] Rabbit syndrome has classically been reported with long-term typical antipsychotic use; however, there are recent case reports with atypical antipsychotics including quetiapine[12] and paliperidone.[13] In addition, withdrawal-emergent[14] and selective serotonin reuptake inhibitor (SSRI)–induced cases[15] have been reported. In addition, rabbit syndrome has most frequently been reported in middle-aged women,[16] consistent with this report.

While an unmasking of TD was considered, TD generally involves significantly slower and less regular movements than was seen in this patient and often involves the tongue. In addition, there was a good response to anticholinergics as has been reported in rabbit syndrome, in contrast to TD, which responds poorly to anticholinergics and occasionally worsens.[17] Furthermore, the concurrent presentation of parkinsonism suggests a hypodopaminergic state in contrast to the predominant hypothesis that TD represents a dopaminergic supersensitivity in the nigrostriatal pathway. Indeed, it has been proposed that rabbit syndrome may be the pathophysiological "converse" of TD and may be more closely related to neuroleptic-induced parkinsonism.[18]

Another issue is whether these symptoms were secondary to the discontinuation of ziprasidone, the initiation of sertraline, or a combination of both. Although antipsychotic withdrawal-induced EPS has generally been reported to occur 2 to 4 weeks after discontinuation,[19] symptoms here appeared within 24 hours suggesting an immediate decrease in dopaminergic tone, possibly suggesting a primary role for sertraline in mediating these symptoms. Indeed, SSRI-induced EPS including sertraline-induced have been well described.[20] It should be noted, however, that this patient had no reported EPS while previously on sertraline monotherapy at doses up to 200 mg/d. It is possible, then, that long-term ziprasidone treatment and/or abrupt withdrawal led to enhanced sensitivity to sertraline-induced EPS.

What might be a theoretical mechanism for this patient's presentation? At low doses, ziprasidone is predicted to have substantial 5-HT_{2A} and 5-HT_{2C} antagonism without significant D_2 antagonism.[1] Blockade of 5-HT_2 receptors increases striatal dopamine release, mediating the reduced EPS liability of ziprasidone and the other atypical antipsychotics. However, chronically increased dopamine release may result in a down-regulation of striatal D_2 receptors, leading to a sensitization to potential EPS. On abrupt discontinuation of ziprasidone, the removal of 5-HT_2 blockade would allow the serotonin-induced inhibition of dopamine release, further decreasing nigrostriatal dopaminergic tone. The addition of serotonin reuptake inhibition, then, by acutely enhancing 5-HT_2 activation, might be expected to exacerbate the dopamine blockade leading to the EPS.

In conclusion, it seems that this patient, who tolerated high-dose sertraline in the past, developed an enhanced sensitivity to sertraline-induced EPS on the abrupt withdrawal of long-term low-dose

ziprasidone treatment. Given the increased use of atypical antipsychotics in mood disorders, this case may serve as caution against abruptly discontinuing ziprasidone and initiating an SSRI.

AUTHOR DISCLOSURE INFORMATION

The author declares no conflicts of interest.

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Treatment of Night Eating Syndrome With Topiramate
Dawn of a New Day

To the Editors:

Research diagnostic criteria for night eating syndrome (NES) were developed in The First International Night Eating Symposium.[1] They include the following: significant increase in energy intake (at least 25%) during the evening/nighttime; evening/nocturnal eating episodes patients are aware of; lack of desire to eat in the morning; strong urge to eat between dinner and sleep or during the night; insomnia most nights; belief one must eat to sleep; and frequent worsening of mood in the evening. Night eating syndrome is more common among obese patients with a prevalence of 6% to 16%[2] compared to (1.5%) in the general population.[3]

Night eating syndrome must be differentiated from binge eating disorder (BED) in which a larger amount of food (than normal) is eaten during a short period of time (within a 2-hour period) along with a sense of lack of control over eating. Additional features include eating rapidly; when not hungry; or alone owing to embarrassment and feeling uncomfortably full, guilty, or disgusted. Night eating syndrome must also be differentiated from the sleep-related eating disorder (SRED) characterized by abnormal eating during the night while still asleep, without any recollection of doing so. Additional features are weight gain, nonrefreshing sleep, and diabetes mellitus.

Successful pharmacological treatment of NES includes medication affecting serotonin modulation[4] with specific evidence for the selective serotonin reuptake inhibitor antidepressant sertraline[5] and topiramate, an antiepileptic. Topiramate has been found efficacious in the treatment of BED in placebo-controlled studies, meta-analyses, and reviews.[6–9] In addition, a small case series by Winkelman[10] reported the efficacy of topiramate in NES and SRED resistant to other pharmacotherapy and psychotherapy. The pharmacodynamic properties of topiramate differ from the selective serotonin reuptake inhibitor and include inhibitory effects on glutamate receptors, Na+ and Ca++ channels, and modulation of GABA receptors.[11]

CASE

A 54-year-old woman with no history of eating disorders, on 150-mg/d venlafaxine treatment for recurrent major depressive disorder, was referred for assessment owing to nocturnal eating associated with weight gain that had developed insidiously over a year. There were chronic stressful interpersonal events in her life, although such events had never precipitated an eating disorder in previous depressive episodes. During this period, she gained 5 kg, constituting a 10% increase in her weight (55–60 kg). Basal metabolic index increased from normal (22.6) to borderline overweight (24.7). On assessment, she fulfilled criteria for NES, and eating patterns could not be attributed to residual depression, medical conditions, or antidepressants. The absence of binges and full awareness of actions ruled out BED and SRED, respectively.

Her main energy intake was in the postmeridian hours. Excessive eating occurred after a well-balanced dinner she cooked herself. She commenced in repetitive compulsive snacking throughout the evening: nibbling at leftovers, cookies, fruit, or sweets. She often postponed bedtime to eat more and at times ate a ceremonial "last snack" in bed. During most nights, she