(2.20 per 1000) as reported by Stephansson et al,[3] our associated sample size was not sufficient to enable adequate statistical power to justify their investigation. We do, however, appreciate the significance of including data on infant mortality to more completely describe the effects of prenatal SSRI exposure on extreme clinical manifestations and the infant life prognosis. In accordance with this, we have included data on stillbirths and neonatal death later.

Our original analysis included the investigation of neonatal outcomes among live-born singletons. After including data on infants previously excluded from the study (ie, fetal deaths), there was only 1 (0.61%; 6.1 per 1000 births) stillbirth in the group of women who received a dispensing for an SSRI, 14 (0.89%; 8.9 per 1000 births) stillbirths in the group of women who had a documented psychiatric illness but did not receive a dispensing for an SSRI, and 198 (0.45%; 4.5 per 1000 births) stillbirths in the group of women who did not have a psychiatric illness and did not receive a dispensing for an SSRI. With recognized limitations of sample size set aside, these differences were not statistically significant.

From the available data, we can confirm that there were 2 (0.90%; 9.0 per 1000 births) neonatal deaths in the group of women who received a dispensing for an SSRI, 5 (0.3%; 3.2 per 1000 births) neonatal deaths in the group of women who had a documented psychiatric illness but did not receive a dispensing for an SSRI, and 96 (0.30%; 3.0 per 1000 births) neonatal deaths in the group of women who did not have a psychiatric illness and did not receive a dispensing for an SSRI. Again, with recognized limitations of sample size set aside, these differences were not statistically significant. Furthermore, no data were available to us in relation to the cause of death.

Given the relatively small number of outcomes, we feel that these results should be interpreted with caution, making it difficult to draw accurate comparisons with previous studies, such as that published by Stephansson et al.[3] An important note is that our overall rates of fatal outcomes in our cohort are higher than what was identified by Stephansson et al.[3] This could be a manifestation of our cohort being derived from a single specialist tertiary level teaching hospital that is likely to attract high-risk pregnancies,[2] as opposed to the population-based approach undertaken by Stephansson et al.[3] We also acknowledge the limitation of not having data available to assess the severity of underlying maternal illness. Further studies with adequate sample size are required to clarify these findings, and we look forward to this evolving literature.

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AUTHOR DISCLOSURE INFORMATION

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Sleep-Related Eating Disorder Associated With Mirtazapine

To the Editors:

Sleep-related eating disorder (SRED) is defined as recurrent episodes of involuntary eating and drinking during arousal from sleep with problematic consequences.[1] Patients are partially or fully amnestic for this eating behavior. The pathophysiologic mechanism of SRED is uncertain but it has been suggested that it may be related to dopaminergic dysfunction. This theory is supported by the increased prevalence of SRED in restless legs syndrome (RLS).[2] Several case reports have been reported in which SRED was associated with zolpidem use.[3–6]

The authors present a case of a patient who showed binge eating behavior after sleep-onset due to mirtazapine treatment. The patient showed complete remission after mirtazapine treatment was discontinued. On the basis of a literature review, this is the first report of SRED linked to the use of mirtazapine.

CASE REPORT

The subject in this case report is a 24-year-old woman who was brought to the psychiatric ward by her parents and was admitted with depressed mood and suicidal gestures (drug ingestion: zolpidem 50 mg). She reported that she had experienced depressed mood, volition loss, and sleep disturbance for several years and had treated her symptoms with fluoxetine (40 mg/d), trazodone (75 mg/d), and zolpidem (10 mg/d) at a local psychiatric clinic she had visited a year ago. Also, she intermittently experienced night binge eating after sleep-onset but could not remember her eating behavior the next morning. Her weight increased from 50 to 70 kg during a period of 6 months. Physical and neurological examinations and all laboratory tests were normal. There was also no evidence of RLS, periodic limb movement disorder (PLMD), and history of other prior parasomnias. Abnormal eating behavior could be associated with zolpidem and fluoxetine combination therapy. Therefore, we discontinued her all medications at intake and replaced them with mirtazapine (30 mg/d) and clonazepam (0.25 mg/d). Her depressive mood, suicidal ideation, and insomnia improved, and her night binge eating episodes disappeared. After 2 weeks of inpatient therapy, she was discharged from the hospital with markedly improved states.

However, 2 weeks after discharge, she reported weight gain and night binge eating episodes (4 weeks of mirtazapine and clonazepam use). She usually received her medications around 11 P.M. and went directly to bed. Approximately 1 to 2 hours after sleep-onset, she arose and ate large amounts of food. She seemed to be awake and showed nervousness and irritability when family attempted to stop her behavior. But she could not remember her unusual eating behavior the next morning.

Even after her mirtazapine dose was reduced to 15 mg/d, her abnormal eating behaviors continued. We finally discontinued mirtazapine, and the binge eating behavior disappeared.

DISCUSSION

For a diagnosis of SRED, a patient must experience recurrent episodes of involuntary eating and drinking with problematic results. These involuntary eating and drinking episodes should include 1 or

more of the following: consumption of peculiar forms of food or toxic substances, insomnia related to sleep disruption with daytime fatigue or sleepiness, sleep-related injury, dangerous behaviors performed while in pursuit of food or while cooking food, morning anorexia, and adverse health consequences from recurrent binge eating of high-caloric foods.[1] Because our patient exhibited recurrent episodes of binge and uncontrollable eating after arousal from sleep, she could not remember her abnormal eating behavior; her symptoms met the diagnostic criteria for SRED. Several drugs, such as zolpidem, triazolam, olanzapine, risperidone, and quetiapine related to SRED,[3–9] and topiramate, clonazepam, and dopaminergics showed therapeutic benefits through case reports and small uncontrolled studies.[10–12]

Mirtazapine enhances serotonin release by blocking α-2 autoreceptors and heteroreceptors, selectively antagonizing the serotonin 5-HT2 and 5-HT3 receptors in the central and peripheral nervous system. Blockade of 5-HT2 and 5-HT3 receptors may produce antidepressant effects by relieving sleep disturbance or increasing appetite. Mirtazapine also has a potent antagonist effect on histamine 1 receptors, which may augment the sedative and appetite-increasing effects.

The pathophysiology of SRED is still unclear. However, because SRED is prevalent in patients with RLS and PLMD, there is evidence that SRED may be related to dopaminergic dysfunction.[2,10,13,14] Some investigators have reported that combined selective α-2 adrenoceptor antagonists and norepinephrine transporter inhibitors caused a marked and selective increase of extracellular dopamine in prefrontal cortex.[15,16]

However, second-generation antidepressants alone may cause RLS in 9% of patients, and mirtazapine induced or exacerbated RLS in 28% of patients.[17] Moreover, recent reports showed an association of mirtazapine with PLMD-like symptoms.[18] Although serotonin-mediated dopamine inhibition might be a mechanism,[19] it is uncertain which mechanism of mirtazapine causes SRED.

Here, we report the first case of mirtazapine-related SRED. The use of mirtazapine should, therefore, be considered a possible precipitating factor for developing SRED, and it will not necessarily have an immediate onset.

AUTHOR DISCLOSURE INFORMATION

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Donepezil-Associated Mania in Two Patients Who Were Using Donepezil Without a Prescription

To the Editors:

More than 40 years ago, it was postulated that excess acetylcholine was associated with depression and decreased acetylcholine was associated with mania.[1] Although the prevailing notion that increased cholinergic status is associated with depression, to date, there are 7 case reports of mania related to the use of donepezil in subjects with dementia.[2–7] Donepezil is a reversible acetylcholinesterase inhibitor, which acts on the nervous system when used in the treatment of dementia of the Alzheimer type. We report the first 2 cases of mania associated with donepezil use in healthy men who took donepezil that was not originally prescribed for them.