Catatonia as a Presenting Feature of Alcohol Withdrawal: A Case Report

Sir: Catatonia is a clinical syndrome characterized by alterations in motor behavior and changes in thought, mood, and vigilance[1] and occurs in a variety of medical and neuropsychiatric conditions.[2] Catatonia has been documented as occurring in alcohol withdrawal in rodents,[3] but not in humans. We report the case of a patient in whom alcohol withdrawal presented as catatonia.

Case report. Mr. A, aged 35 years, presented in January 2006 with a history of alcohol use over the last 10 years. He fulfilled the DSM-IV criteria for alcohol dependence for the last 5 years.

He presented with tremors, irritability, anorexia, and insomnia within 24 hours of abrupt cessation of alcohol intake. Seventy-two hours after cessation of alcohol intake, he developed signs of negativism, mutism, and psychomotor agitation lasting 2 days, followed by psychomotor retardation, stereotypies, and stupor over the next 2 days, fulfilling DSM-IV criteria for catatonia. There were no psychotic or mood symptoms, clouding of consciousness, disorientation, or any general medical condition that could explain these symptoms.

He had experienced a similar episode 2 years previous, following 3 days of abstinence from alcohol, that remitted upon treatment with lorazepam. Family history was positive for alcohol dependence in first- and second-degree relatives but was negative for psychotic or mood disorders. The findings of laboratory investigations were within normal limits.

As the patient's condition could not be described adequately by DSM-IV criteria for alcohol withdrawal or catatonia, the diagnosis of alcohol-induced psychotic disorder was made, with onset during alcohol withdrawal and presenting with catatonia. Mr. A was treated with lorazepam 16 mg per day and with vitamin supplements. His symptoms remitted completely within 72 hours.

Catatonia has been documented in alcohol dependence in relation to drug interactions involving disulfiram[4] and in delirium.[1] The temporal correlation between alcohol abstinence and the appearance of catatonia in the absence of these other causes suggests that the catatonia in this case was due to alcohol withdrawal. Perturbations in γ-aminobutyric acid (GABA)-ergic and glutamatergic transmission have been implicated in the pathophysiology of both catatonia[2] and alcohol withdrawal.[5,6] Furthermore, the $GABA_A$ modulator lorazepam is effective in both conditions.[1,7] To our knowledge, this case is the first such case reported in the literature.

The authors report no financial or other affiliations that can be considered a conflict of interest relevant to the subject of this letter.

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Monocytosis Subsequent to Ziprasidone Treatment: A Possible Side Effect

Sir: Ziprasidone is an atypical antipsychotic agent that is available as oral and short-acting intramuscular formulations and is approved by the U.S. Food and Drug Administration for management of schizophrenia and bipolar disorder. Ziprasidone acts as a serotonin and dopamine receptor antagonist, with greater affinity for the $5\text{-}HT_{2A}$ receptor than the dopamine D_2 receptor.[1] Moreover, it possesses agonist activity at the serotonin $5\text{-}HT_{1A}$ receptor.[1] The low affinity of ziprasidone for α-adrenergic, histaminergic, and muscarinic receptors favors a good safety and tolerability profile. Commonly observed side effects are often negligible and include metabolic effects, QTc prolongation, and movement disorders.[2]

Here, we report the case of a schizophrenia patient with monocytosis subsequent to ziprasidone monotherapy.

Case report. Mr. A, a 22-year-old man, was admitted to the hospital in 2006 with a first episode of paranoid schizophrenia (DSM-IV criteria). The patient had no history of psychiatric or neurologic illness. Drug screening, magnetic resonance imaging, lumbar puncture, and routine laboratory testing including blood count, C-reactive protein, and liver enzymes (alanine aminotransferase, aspartate aminotransferase) were unremarkable.

We started therapy with olanzapine 20 mg/day. However, at day 10, routine laboratory testing detected increased liver enzymes, and ultrasound showed hepatomegaly, so olanzapine treatment was therefore stopped. After termination of medication, Mr. A's liver enzymes normalized promptly, and hepatomegaly resolved during the next 7 days. Subsequent to normalization of diagnostic findings, we started treatment with ziprasidone 160 mg/day. However, the next routine laboratory testing, on day 7 of treatment with ziprasidone 160 mg/day, showed an isolated monocytosis, with a monocyte level of > 1.35 ($\times 10^9$/L). Laboratory tests at days 14 and 21 of treatment with ziprasidone 160 mg/day confirmed monocytosis. Liver enzyme levels, sonography, C-reactive protein levels, blood cultures, urine culture, urinalysis, electrolyte levels, and chest x-ray were unremarkable, and clinical examination revealed no infection signs. Due to the observations of

monocytosis, we initiated a detailed hematologic and hepatologic workup. Alcoholic, viral, immunologic, and cancerous reasons were excluded, and our hematologic and hepatologic consultants diagnosed a medication-induced process.

After 28 days, ziprasidone treatment was stopped, and risperidone treatment was initiated. The next laboratory tests, on day 7 after completion of ziprasidone treatment, detected a declining monocyte level of < 0.85 ($\times 10^9$/L). Measurements of serum olanzapine and ziprasidone never showed elevated levels.

After exclusion of other symptomatic causes, the close temporal relationship between monocytosis and onset of ziprasidone medication and the disappearance of this condition with termination of therapy with the drug argue against a natural course and support the assumption that monocytosis was induced by ziprasidone. It remains debatable if the observed effect has any clinical relevance or is only a transient phenomenon. However, to our knowledge, ziprasidone-induced monocytosis has not yet been reported.

Moreover, this case again highlights the known and mostly transient phenomenon of liver enzyme increase and hepatomegaly subsequent to olanzapine treatment and demonstrates the importance of regular laboratory tests, including liver enzymes, during medication with atypical antipsychotics.

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Escitalopram in Obsessive-Compulsive Disorder: A Case Series

Sir: Obsessive-compulsive disorder (OCD) is a chronic and debilitating psychiatric disorder. The lifetime prevalence of OCD is estimated to be 1.94% to 3.29% according to population-based surveys.[1–3] Serotonin reuptake inhibitors (SRIs) are known to be effective in OCD.[4–6] However, 50% to 60% of OCD patients may not respond to the first SRI but will respond to another SRI. Hence, sequential trials of SRIs are considered.[7]

Escitalopram is the pure *S*-enantiomer (single isomer) of the racemic, bicyclic, phthalane derivative citalopram. Escitalopram has been approved by the U.S. Food and Drug Administration for use in major depressive disorder and has also been used in various anxiety disorders such as generalized anxiety disorder, social anxiety disorder, and panic disorder.[8] There are studies reporting the efficacy of citalopram in OCD.[9,10] The available data suggest that escitalopram possesses advantages over citalopram in terms of both efficacy and safety.[11]

A search of MEDLINE and PubMed using the keywords *obsessive-compulsive disorder* and *escitalopram* retrieved no published reports or articles. Herein, we describe cases of 3 patients with OCD who had never been treated with selective SRIs, with illness duration ranging from 3 to 30 years, and who responded to treatment with escitalopram. Informed consent was given by the patients before starting treatment with escitalopram.

Case 1. Ms. A, a 60-year-old housewife of middle-class socioeconomic status and urban background, presented to our hospital in June 2006 with an insidious onset and continuous course of 30 years' duration that was characterized by obsessive and compulsive symptoms. She had a well-adjusted premorbid personality and a family history of nonaffective psychosis in a younger brother.

Structured assessment using the Mini-International Neuropsychiatric Interview (MINI-Plus)[12] revealed that she had had 2 episodes of depression in the past, characterized by sadness of mood, increased fatigability, anhedonia, ideas of guilt, reduced concentration, and impaired biological and social functioning. She had received treatment with dothiepin 75 mg/day with much improvement in depression but not in obsessive-compulsive symptoms. During the current assessment, she had no depressive symptoms but fulfilled the diagnostic criteria for OCD. The Yale-Brown Obsessive Compulsive Scale (YBOCS)[13,14] checklist showed obsessions of contamination, aggression, and religion and compulsions of cleaning and checking. Baseline assessment revealed a YBOCS severity rating total score of 26 (obsession 12, compulsion 14), a Clinical Global Impressions-Severity of Illness (CGI-S)[15] score of 4 (severely ill), and a YBOCS-11 (item 11) insight score of 1 (good insight).

Ms. A was started on treatment with escitalopram 10 mg/day, which was increased to 25 mg/day. At 3-month follow-up, the patient's YBOCS severity total score was 10 (obsession 5, compulsion 5), her CGI-S score was 2 (borderline mentally ill), and her CGI-Improvement (CGI-I)[15] score was 2 (showing much improvement).

Case 2. Mr. B, a 26-year-old unemployed, unmarried man of middle-class socioeconomic status and rural background, presented to our hospital for the first time in August 2006 with an illness of 3 years' duration, with insidious onset and continuous course and characterized by obsessions of contamination, doubts, and sexual content, followed by compulsions of washing, checking, and mental rituals. His personal history and family history were noncontributory. His premorbid personality revealed that he was shy and reserved, avoiding social situations, and had few friends.

Structured assessment with the MINI-Plus revealed comorbid diagnoses of dysthymia and social phobia along with mixed obsessive-compulsive disorder. Baseline assessment revealed a YBOCS severity rating total score of 24 (obsession 14, compulsion 10), a CGI-S score of 4 (severely ill), and a YBOCS-11 insight score of 2 (fair insight).

Mr. B was started on treatment with escitalopram 10 mg/day, which was increased to 20 mg/day. At 3-month follow-up, the patient's YBOCS severity total score was 11 (obsession 6, compulsion 5), his CGI-S score was 2 (borderline mentally ill), and his CGI-I score was 2 (much improvement). It is interesting to note that during follow-up he did not meet the criteria for social phobia on the MINI-Plus.

Case 3. Mr. C, a 34-year-old unemployed, married man of middle-class socioeconomic status and urban background, presented for the first time in August 2006 with an illness of 7 years' duration, with insidious onset and continuous course and characterized by complaints suggestive of obsessive doubts,

sexual obsessions, and obsessions regarding need for symmetry. He also had checking compulsions, repeating rituals, and ordering compulsions. His premorbid personality was well adjusted, and he reported noncontributory personal and family histories.

After structured assessment with the MINI-Plus, he was diagnosed with OCD, mixed subtype. His baseline YBOCS severity rating total score was 29 (obsession 15, compulsion 14), his CGI-S score was 5 (markedly ill), and his YBOCS-11 insight score was 2 (indicating that he had fair insight into his problems).

Mr. C was started on treatment with 10 mg/day of escitalopram, which was increased to 20 mg/day. During his 3-month follow-up assessment, his YBOCS severity total score was 14 (obsession 9, compulsion 5), his CGI-S score was 2 (borderline mentally ill), and his CGI-I score was 2 (much improvement).

The 3 cases of OCD presented above had a duration of illness ranging from 3 to 30 years and were assessed with a structured instrument, indicating a stable diagnosis. During intake and follow-up of the patients, at least 1 qualified psychiatrist, who is a consultant in an OCD clinic, did the ratings of YBOCS severity and the CGI scales. All 3 patients responded to treatment with escitalopram: YBOCS scores dropped by more than 50%, CGI-S scores showed all patients to be "borderline mentally ill," and there was "much improvement" on the CGI-I scale.

Currently, clomipramine, fluoxetine, sertraline, fluvoxamine, paroxetine, and citalopram have been clearly documented to be effective in OCD.[4–6] Choice of SRI in treatment of OCD is largely based on side effect profile and comorbid medical/psychiatric conditions.[16] Available data on escitalopram reveal that it has minimal drug interaction and is well tolerated in depressed patients in primary care.[17] Hence, it can be used safely in OCD patients with comorbid medical/psychiatric conditions. It is interesting to note that 1 patient reported improvement even in social phobia. The other 2 patients had no current comorbid conditions during intake. Thus, improvement in OCD was not related to improvement in comorbid conditions, and use of the YBOCS severity scale clearly documented the improvement in OCD symptoms. This case series assumes importance in light of the relative paucity of escitalopram studies in OCD. Escitalopram is known to be well tolerated and to have few interactions with other drugs, and these benefits provide a boon for our OCD patients. Double-blind, placebo-controlled studies examining the efficacy of escitalopram in OCD are needed.

The authors report no financial or other affiliations that can be considered a conflict of interest relevant to the subject of this letter.

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Hypothyroidism in Patients With Asthma and Major Depressive Disorder

Sir: Approximately 8% of depressed patients have at least subclinical hypothyroidism,[1] compared to only 5% of the general population.[2] An epidemiologic study found that hypothyroidism may also be associated with asthma,[3] although this association is less well established than the association with depression. Depression is extremely common in asthma patients.[4] Thus, depressed asthma patients may be a population at especially high risk for hypothyroidism. To our knowledge, no data are available examining thyroid abnormalities in depressed asthma patients. This study evaluated the relationship between depression, thyroid disease, and asthma severity in asthma patients with current depression.

Method. This investigation examined 90 participants with asthma and major depressive disorder (MDD) from a clinical trial conducted between March 2002 and December 2003 on the treatment of depression in asthma patients.[5] The study received institutional review board (IRB) approval, and all participants provided IRB-approved informed consent. Adult outpatients

who had asthma and current MDD with a 17-item Hamilton Rating Scale for Depression (HAM-D)[6] score of at least 17 were included in this study. No participants were taking medication for depression at the time of assessment.

Major depressive disorder was diagnosed using the Mini-International Neuropsychiatric Interview.[7] Thyroid disease was diagnosed using both clinical history (e.g., physician diagnosis of hypothyroidism and patient taking thyroid supplementation) and laboratory analysis of thyroid-stimulating hormone (TSH) levels; TSH levels were obtained at study enrollment. Asthma symptoms were assessed using the Asthma Control Questionnaire (ACQ).[8] Two-tailed t tests and Pearson correlations were used to determine significance.

Results. This investigation examined the history of thyroid disease in 90 participants. The participants were 78.7% female with a mean ± SD age of 40.1 ± 10.2 years; 6.7% were white, 58.2% were Hispanic, and 33.3% were African American; and the group had a mean ± SD forced expiratory volume in 1 second percentage (FEV_1%) predicted of 73.4 ± 20.9%.

Four (4.4%) of the 90 patients had a clinical history of hypothyroidism, and 1 (1.1%) had a history of hyperthyroidism, making the total prevalence rate of a clinical history of thyroid disease 5.5%. Of these 90 participants, 75 were included in the analysis of TSH values. Eleven participants were excluded because baseline TSH scores were not available, and 4 were excluded because they were taking thyroid supplementation that would artificially suppress TSH levels. The 4 participants excluded based on the use of thyroid supplementation were the 4 participants with a history of hypothyroidism discussed above.

Mean ± SD TSH level was 1.9 ± 1.2 mIU/L (range, 0.18–6.10 mIU/L). Of the 75 patients analyzed, 7 patients (9.3%) had TSH levels outside the normal range (0.5–5.5 mIU/L), including 2 patients (2.7%) with high values and 5 patients (6.7%) with low values. A total of 2 (2.7%) of 75 patients showed hypothyroidism based on TSH levels. Therefore, combining information obtained from the 4 participants with a clinical history of hypothyroidism and the 2 participants with elevated TSH levels, the lifetime prevalence rate of hypothyroidism in our population was 6 of 90 patients, or 6.7% (95% CI = 3.1 to 13.8).

No significant correlation was found between TSH levels and HAM-D scores ($r = 0.03$, $p = .82$). Asthma Control Questionnaire scores, however, showed a significant negative correlation with TSH values ($r = –0.24$, $p = .04$).

Hypothyroidism, based on combined clinical history data and elevated TSH values, was found in 6.7% of patients with MDD and asthma. This finding is similar to that reported in general samples of MDD patients. Therefore, asthma does not appear to increase the risk of hypothyroidism in MDD.

Of note is that 5 participants had low TSH values without taking thyroid supplementation. The clinical significance of this finding is difficult to interpret without triiodothyronine (T_3) and free thyroxine (FT_4) data, but possible explanations include subclinical hyperthyroidism,[9] central hypothyroidism, euthyroid sick syndrome,[10] and recent use of oral corticosteroids.[11] Thus, the prevalence of either hyperthyroidism or hypothyroidism may actually be slightly higher than reported.

Thyroid-stimulating hormone levels were not related to depression severity. However, a significant negative correlation was found between ACQ values and TSH levels, suggesting a potential association between asthma control and TSH levels.

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New-Onset Transient Hallucinations Possibly Due to Eszopiclone: A Case Study

Sir: Eszopiclone is one of the newer nonbenzodiazepine hypnotics with a favorable efficacy and safety profile and has received increased attention due to less abuse potential and residual effects.[1] However, rare adverse effects such as hallucinations have been described with other nonbenzodiazepine hypnotics such as zolpidem and zaleplon.[2–5] A case of a patient developing transient visual and auditory hallucinations with eszopiclone is described.

Case report. Mr. A, a 45-year-old white man, was admitted in October 2006 for acute psychotic symptoms of 1 day's duration. Mr. A had recently begun working the night shift at his job (11 p.m. to 7 a.m.) and noticed difficulty sleeping after returning home from work. About a week before his admission, he

was started on eszopiclone treatment by his primary care physician at a dose of 3 mg/day to be taken at about 9 a.m. However, each day Mr. A had to wake up after only a few hours to pick up his children from school.

His sleep pattern became very erratic for the week preceding his hospitalization, and he was getting an average of only 4 hours of sleep per day. The day before his admission, Mr. A had taken eszopiclone before going to bed after returning from work. When he awoke from his sleep as usual to pick up his children, he began seeing flashes of light and hearing whispers and noises. These hallucinations persisted for the next several minutes while the patient was fully awake. He denied any concomitant confusion or delusions. He immediately went to his primary care physician, who recommended that he be admitted to the psychiatric unit for observation.

Upon admission, Mr. A had an unremarkable physical and neurologic examination, and there was no evidence to suggest delirium. He had no past personal or family history of psychiatric illness. Blood counts, serum chemistry (including liver and renal function tests), and urine drug screen were noncontributory. His other medications (doses of which remained unchanged) included hydrocodone/acetaminophen 5 mg/500 mg per day, amlodipine 10 mg/day, lansoprazole 30 mg/day, and simvastatin 40 mg/day. While in the hospital, Mr. A did not need antipsychotics, but he did receive a 3-mg dose of eszopiclone at bedtime that night. He slept well for about 8 hours and did not complain of any hallucinations for the entire next day. Mr. A was discharged that same day.

A PubMed search using the key words *eszopiclone*, *zopiclone*, and *hallucinations* yielded no reports of hallucinations associated with eszopiclone. A similar literature search was unfruitful for possible drug interactions between the patient's other prescribed medications and eszopiclone leading to this adverse effect. Incidentally, the premarketing data in the package insert of eszopiclone list the incidence of hallucinations as 1% and 3% with the 2-mg and the 3-mg dose, respectively, suggesting a dose-response relationship.[6] Psychotic symptoms, including delusions, have been described with nonbenzodiazepine hypnotics such as zolpidem and zaleplon.[2–5,7] Of interest, zolpidem-induced hallucinations have been reported in patients who woke up after taking the medication, a scenario similar to this case.[3] Therefore, drug-related hypnopompic hallucinations are also a possible explanation.

According to the *Physicians' Desk Reference*,[8] hypnotics, including eszopiclone, should not be taken if one is unable to get 8 or more hours of sleep before becoming active again. This directive raises the question of the safety of hypnotics for treating the shift-work type of circadian rhythm sleep disorder. Individuals with this type of disorder may not get enough hours of sleep because of social and domestic demands.[9] In addition, a study showed that zolpidem, though improving subjective sleep quality in night-shift workers, worsened their mood.[10] Taken together, these observations call for more research to ascertain the safety of nonbenzodiazepine hypnotics in circadian rhythm sleep disorder, particularly the shift-work type.

Also, the neuropsychiatric adverse effects associated with nonbenzodiazepine hypnotics have been mentioned in the premarketing data but are rarely discussed with patients. These adverse effects include more outgoing and aggressive behavior, confusion, agitation, hallucinations, worsening of depression and suicidal thoughts, depersonalization, and amnesia.[6,8] As the prescribing of nonbenzodiazepine hypnotics increases, greater awareness among clinicians of these adverse effects is desirable.

Dr. Duggal reports no financial or other relationships relevant to the subject of this letter.

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Two Cases of Compulsive Buying Behavior in Mentally Challenged Persons

Sir: Compulsive buying disorder (CBD) is characterized by excessive shopping cognitions and buying behaviors that lead to distress or impairment.[1] Found worldwide, the disorder has a lifetime prevalence of 5.8% in the U.S. general population.[2] Subjects with CBD report a preoccupation with shopping, prepurchase tension or anxiety, and a sense of relief following a purchase.[3] To our knowledge, there are no reports of compulsive buying in mentally challenged persons. We now report 2 cases of CBD in persons with IQs under 70.

Case 1. Ms. A, a 46-year-old woman who lived with her ex-husband and 2 sons, was referred for treatment of recurrent depression and anxiety in 2006. As part of a comprehensive assessment, she was tested and found to have a full scale IQ of 68. In exploring her sources of stress and anxiety, she disclosed a history of excessive shopping and spending that had led the family to declare bankruptcy and had contributed to her recent divorce (for the second time from the same husband). Her ex-husband had complained that she had a "buying illness" that led her to purchase excessive amounts of clothing (including hundreds of T-shirts), jewelry, and electronic goods—mainly cellular phones—which she neither needed nor used. She acknowledged feeling out of control, and felt unable stop the inappropriate behavior. To deal with her shopping addiction, her ex-husband took her credit card and gave her a weekly allowance. With only the limited weekly allowance, her buying gradually came under better control. Her mother was reported to be a compulsive shopper.

Case 2. Mr. B, a 16-year-old boy, had never learned to read or write and had an estimated IQ between 50 and 60. He was referred for evaluation for overspending and frequent tantrums in 2006. The excessive spending had begun a year earlier after he took a part-time job. With his new income, Mr. B had become preoccupied with buying "presents" for himself, including many cellular phones, and inappropriate and excessive amounts of clothing. While the buying behavior made him feel important, his parents were concerned, but their attempts to control his spending only led to loud arguments and tantrum-like behaviors in which he would destroy property, such as his cellular phones. There were no signs of depression or mania, nor was there a history of substance misuse.

In summary, to our knowledge, this is the first report of persons with subnormal IQs who presented with CBD. In both cases, there was evidence of uncontrolled shopping and spending that led to financial distress and contributed to family or marital problems. In neither case could the CBD be attributed to mania or hypomania. Their CBD appeared to be descriptively identical to that observed in other subjects who are not mentally challenged.

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Venlafaxine-Induced Manic Switch in an Adolescent Patient: A Case Report

Sir: Venlafaxine is a serotonin-norepinephrine reuptake inhibitor approved for the treatment of major depressive disorder by the U.S. Food and Drug Administration.[1] There is evidence to show that it causes manic switch in adult patients.[2,3] However, data regarding the manic switch in adolescents are sparse. A PubMed (MeSH database) search using the keywords *venlafaxine*, *bipolar disorder*, and *adolescent* retrieved no studies or case reports. Hence, we are reporting a case of venlafaxine-induced manic switch in an adolescent patient.

Case report. Ms. A, a 17-year-old girl, presented to our clinic in 2004 with 5 months' history of pervasive sadness of mood with early morning worsening, social withdrawal, anhedonia, easy fatigability, terminal insomnia, anorexia, crying spells, inability to concentrate in studies, slowness in daily activities, ideas of helplessness, and death wishes. She stopped attending school 4 weeks before reporting to our hospital. The patient was diagnosed to have major depressive disorder, single episode, severe with melancholic symptoms per DSM-IV criteria. Venlafaxine therapy was started at 37.5 mg/day that was gradually increased to 150 mg/day over 2 weeks. She had no past history or family history of psychiatric illness. Her biochemical and hemogram parameters were within normal limits.

During her first follow-up at the end of 4 weeks of venlafaxine treatment, she was noted to be irritable at trivial issues and reported pervasive elated mood, increased energy levels, increased speech output, decreased need for sleep, increased goal directed activity, racing thoughts, expansive ideas, and disruptive behavior. She was also noticed to exhibit disinhibited behavior, singing and dancing. Her disruptive and disinhibited behavior was noted to have been present during the preceding 2 to 3 weeks. She met DSM-IV criteria for mania.

Her symptoms were severe, warranting admission. During in-patient treatment, venlafaxine was stopped. There was no improvement for the next 4 days. Hence, the treating team decided to add risperidone (1 mg/day) and valproate (750 mg/day increased to 1500 mg/day) considering her severity of symptoms. She reached a euthymic state during the next 8 weeks; risperidone was discontinued over the next 4 weeks, and she has remained euthymic during the last 6 months while on valproate therapy.

This patient had no risk factor for bipolarity, viz., no past or family history. The switch to mania occurred within 4 weeks of starting venlafaxine treatment, which suggests venlafaxine-induced mania. She met the criteria for antidepressant-induced switch delineated by Altshuler and others in 1995.[4] Given this risk of manic switch with venlafaxine, we recommend that clinicians be cautious in administering venlafaxine, especially in adolescents.

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

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Onset of Obstructive Sleep Apnea After Initiation of Psychotropic Agents

Sir: Obstructive sleep apnea (OSA) is a condition manifested by overall hypoxia of major body systems. The following case is an illustration of several interesting connections between OSA and the utilization of various psychopharmacologic agents.

Case report. Mr. A, a 35-year-old married white male, was diagnosed with DSM-IV posttraumatic stress disorder related to several exposures to occupationally related trauma, depression, and anxiety. In addition, he has chronic pain related to multiple fractures. He was started on fluoxetine, 20 mg/day, along with lorazepam, 0.5 mg p.r.n. Subsequently, approximately 6 months later, Mr. A gained 35 pounds, developed OSA, and was diagnosed with hypertension. Fluoxetine treatment was continued for 3 additional months but was then discontinued; lorazepam treatment was continued. Currently, he additionally receives treatment with continuous positive airway pressure and antihypertensives and complains of loss of libido.

While metabolic syndrome has been observed in cases in which individuals are taking some atypical antipsychotics[1] and OSA in cases involving depression,[2] the development of metabolic syndrome accompanying the use of the newer antidepressants[3] or atypical antipsychotics is a phenomenon that has rarely been reported. Only 1 study to date[4] has explored the association of depression, psychotropics, and OSA. The group reported a bidirectional relationship with a prevalence of 18%. Observations with sleep study confirmations (11 patients) in our own practice during 2007 showed a comorbidity of OSA during treatment with novel antidepressants, particularly those involving the regulation of serotonin, and weight gain is becoming increasingly apparent in these antidepressant-treated patients who have developed OSA. One might speculate that the rapid weight gain often associated with the initiation of a selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor leads to OSA, but the firm association of this cascade of events needs to be more scientifically established.

The implications in terms of cost alone nationally for treating OSA are staggering. Furthermore, as OSA possibly resulting from weight gain causes hypoxia and poor sleep, a disruptive cycle of decreased health status and continued if not exacerbated depression may evolve.

At the very least, it behooves us as clinicians and scientists to examine whether there is as clearly defined a relationship between the use of antidepressant medications of a certain class and OSA (mitigated or not by associated weight gain) as currently exists among some atypical antipsychotics, weight gain, and metabolic syndrome.

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Lamotrigine-Induced Neutropenia in a Woman With Schizoaffective Disorder

Sir: Lamotrigine is a drug of the phenyltriazine class with inhibitory effects on voltage-sensitive sodium channels along with modulating effects on calcium and potassium channels. Lamotrigine is also a weak dihydrofolate reductase inhibitor. The drug is currently approved by the U.S. Food and Drug Administration for maintenance treatment in bipolar type I disorder. There have been reports of hematologic adverse effects with lamotrigine therapy.[1–8] We report a case of a 50-year-old woman with schizoaffective disorder who presented with neutropenia while on lamotrigine therapy.

Case report. Ms. A, a 50-year-old African American woman with DSM-IV schizoaffective disorder, presented in 2003 with mood swings, alopecia, and weight gain during treatment with 1000 mg/day of sodium valproate therapy. After a discussion of available choices, a decision to cross-taper and switch her to lamotrigine was made. Lamotrigine was initiated at 12.5 mg once daily for 2 weeks and was increased to 25 mg once daily for 2 weeks and then increased by 50 mg every 2 weeks until she was receiving lamotrigine 150 mg twice daily. Sodium valproate was tapered over a week. The patient tolerated the switch well and reported a significant improvement in mood symptoms. Her white blood cell (WBC) count and absolute neutrophil count (ANC) prior to lamotrigine therapy were 4.9×10^9/L (reference range, $4–11 \times 10^9$/L) and 2.8×10^9/L (reference range, $1.7–7 \times 10^9$/L), respectively.

However, 2 months later, a routine complete blood cell (CBC) count revealed a WBC count of 3.8×10^9/L and an ANC count of 2.2×10^9/L. Ms. A did not demonstrate any clinical signs or symptoms of leukopenia, and the rest of her laboratory results were unremarkable. Medical illnesses and medications associated with leukopenia were ruled out. On the basis of her robust therapeutic response to lamotrigine and the lack of clinical signs and symptoms of neutropenia, a decision to continue lamotrigine therapy was made. Regular CBC counts were obtained to monitor the leukopenia.

Approximately 4 months later, based on declining blood counts, a decision to decrease lamotrigine by 50 mg/day was made. Following the dose reduction, her counts briefly went back to baseline level; however, they soon resumed a downward trend. Finally, a decision to discontinue lamotrigine was made after Ms. A had been on treatment with the drug for approximately 10 months. Her WBC count and ANC at drug discontinuation were 2.8×10^9/L and 1.5×10^9/L, respectively. Subsequent WBC count and ANC readings returned to baseline level in a few weeks without any recurrence of neutropenia.

Approximately a year and half later, Ms. A moved to another state, where a retrial of lamotrigine 100 mg once daily was attempted. At that time, her leukocyte and neutrophil counts decreased from 3.5×10^9/L and 1.9×10^9/L before therapy to 2.6×10^9/L before therapy to 1.5×10^9/L after 2 months of lamotrigine therapy. Again, after drug discontinuation, her counts returned to baseline over a period of approximately 6 weeks. Her counts have been stable since then. While the patient was receiving lamotrigine, hematologic adverse effects from concomitant medications or medical conditions were ruled out. The platelet counts and red blood cell counts remained within normal limits throughout this period.

Published reports of lamotrigine-induced neutropenia[1–4] and agranulocytosis[5–8] have demonstrated normalization of blood counts with drug discontinuation alone. In our case, there was a definite association between lamotrigine therapy and neutropenia. The brief normalization of blood counts following dose reduction of lamotrigine and the on-off-on trial further support the cause-and-effect relationship. Other risk factors for lamotrigine-induced hematologic adverse effects such as concomitant anticonvulsants or exceeding the recommended starting dose or titration were absent in our case. Although our patient was African American, benign ethnic neutropenia was an unlikely cause of the observed effect as the variations in counts were observed with drug rechallenge and discontinuation.

Although the mechanism of action of lamotrigine-induced hematologic abnormalities is unknown, a combination of immunoallergic, direct medullary toxicity, and granulopoiesis-inhibiting effects has been suggested.[1] There are also reports on lamotrigine-associated macrocytic anemia,[9] leukopenia,[10–12] and thrombocytopenia,[12] which suggest a common possible mechanism involving enzymatic inhibition of dihydrofolate reductase by lamotrigine. It is plausible that one or more of the above pathophysiologic mechanisms were involved in our patient. With the normalization of blood counts with discontinuation alone, we did not attempt a bone marrow aspiration.

Our case demonstrates a combination of unique features: a dose-dependent variation in WBC count and ANC, gradual development of neutropenia, as well as the outcome of a rechallenge. To our knowledge, these features have not been reported in the same patient. In any event, our case report provides more evidence to corroborate this rare but dangerous side effect and emphasizes the need for frequent monitoring of blood counts during lamotrigine therapy.

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