Pregabalin Augmentation to Sertraline-Risperidone Combination in the Treatment of Obsessive-Compulsive Disorder

Sir: Despite the marked progress in the pharmacologic treatment of obsessive-compulsive disorder (OCD)—especially with high doses of serotonin reuptake inhibitors (SRIs), alone or in combination with low doses of antipsychotics—a substantial proportion of patients fail to respond to it.[1] In such cases, an augmentation tactic with drugs from other chemical classes, including antiepileptic drugs, seems advisable. We report on such a case, in which the adjunction of the newer antiepileptic drug pregabalin led to a patient's marked improvement.

Case report. Ms. A, a 35-year-old woman, had suffered from OCD according to DSM-IV criteria[2] since the age of 10, with a severe exacerbation at the age of 30 and a continuous, unremitting course thereafter. During the last 5 years, she had been prescribed in adequate dosages 5 different regimens combining SRIs with antipsychotics, with only minimal and transient improvement. On admission in April 2007, Ms. A was receiving sertraline 400 mg/day, risperidone 2 mg/day, and clobazam 20 mg/day. She scored 35 on the Yale-Brown Obsessive Compulsive Scale (YBOCS),[3] with an overall severity scale score of 4, whereas on the Hamilton Rating Scale for Anxiety (HAM-A),[4] she scored 27.

Both sertraline and risperidone were maintained at the previously mentioned dosages, whereas clobazam was discontinued. Pregabalin was added to her regimen instead and titrated up to 600 mg/day within 3 weeks. Dizziness and fatigue were the only transient side effects of pregabalin. During pregabalin treatment, Ms. A's mental and behavioral state improved progressively, and at discharge, 12 weeks later, her scores on the YBOCS and HAM-A had dropped by almost 55% and 40%, respectively. More precisely, her YBOCS score dropped to 16, with an overall severity score of 2 and an overall improvement score of 5, and her HAM-A score dropped to 15. Of note, the patient's level of improvement was wholly preserved at her last outpatient appointment 6 months later.

To the best of our knowledge, this is the first case report of administration of pregabalin as an adjunctive treatment to a SRI-antipsychotic combination in OCD refractory to standard pharmacotherapy. Pregabalin, a newer antiepileptic drug, binds to the $\alpha_2\delta$ subunits of voltage-dependent calcium channels, blocking the calcium influx in presynaptic excitatory neurotransmitters such as glutamate, thus dampening excitatory neurotransmission in various brain systems. This mechanism of action accounts for the well-established antiepileptic and antianxiety effects of pregabalin.[5] With respect to pregabalin's specifically anti-OCD mechanism of action, we should note that increased glutamatergic neurotransmission is hypothesized to underlie the increased activity of the cortico-striato-thalamic system, which presumably constitutes the core pathophysiologic mechanism of OCD symptoms.[6]

Although admittedly anecdotal and thus requiring replication in well-designed large studies, the findings of the present report provide supportive preliminary evidence for the potential of pregabalin to ameliorate OCD symptomatology, at least as an adjunctive treatment in patients refractory to standard pharmacotherapy.

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A Case of Lamotrigine-Associated Anticonvulsant Hypersensitivity Syndrome

Sir: Anticonvulsant hypersensitivity syndrome is a potentially life-threatening complication of phenytoin, carbamazepine, and phenobarbital therapy. It has also recently been associated with lamotrigine, a relatively new anticonvulsant used in the maintenance treatment of bipolar depression. We report a putative case of anticonvulsant hypersensitivity syndrome due to lamotrigine that went unrecognized in primary care, dermatologic, psychiatric, and emergency department settings in a 30-year-old woman with bipolar I disorder (DSM-IV-TR).

Case report. Ms. A, a 30-year-old white woman with a history of major depressive disorder, began lamotrigine therapy in February 2006 following a manic episode that resulted in a rediagnosis of bipolar I disorder (DSM-IV-TR). Apart from her psychiatric history, she had no significant past medical history and no known drug or food allergies. Four weeks after initiating therapy, the dosage was increased from 25 mg/day to 50 mg/day. Two days after this increase, Ms. A was seen in a dermatology clinic with a pruritic perioral rash and was diagnosed with contact dermatitis. The following week, she was seen by her primary care physician for fever, cough, oral ulcers, and a spreading facial eruption. Ms. A was prescribed azithromycin and acetaminophen for a presumed upper respiratory infection.

Three days later, Ms. A presented to the dermatology clinic with a fine maculopapular rash on her trunk and extremities. Her cough had worsened, and she had developed swollen lips, ulceration of her inner labia, and emotional instability. A skin biopsy showed dermal-epidermal interface

changes, necrotic keratinocytes, and infiltrating eosinophils, interpreted as a dermal hypersensitivity reaction. She was referred to the emergency department following suicidal ideation in the clinic.

In the emergency department, the patient was afebrile, with normal vital signs. A throat culture and viral respiratory culture were later found to be negative, and a chest x-ray was unremarkable. A complete blood count demonstrated 770 eosinophils/μL (normal value < 500 eosinophils/μL). After an evaluation by the consultation-liaison psychiatry team, the possibility of a nonspecific drug allergy was established. Lamotrigine and azithromycin were discontinued, and the patient was discharged. Anticonvulsant hypersensitivity syndrome, although present, had not been previously recognized, so laboratory studies that might have confirmed the presence of this condition, such as liver function tests and renal studies, had not been ordered.

Over the next 3 weeks, the fever, pharyngitis, malaise, and rash persisted, and Ms. A returned to the emergency department. Electrolytes, blood urea nitrogen, creatinine, and a complete blood count with differential were found to be within normal limits. The patient was given reassurance and discharged with no evidence of a worsening adverse drug reaction.

Anticonvulsant hypersensitivity syndrome is a drug reaction classically caused by the antiepileptic drugs phenytoin, phenobarbital, and carbamazepine, and it has recently been linked with lamotrigine.[1] Anticonvulsant hypersensitivity syndrome is a clinical diagnosis featuring fever, rash, and internal organ involvement. The rash can evolve to Stevens-Johnson syndrome or the potentially fatal complication of toxic epidermal necrolysis.[2] Clinical findings include lymphadenopathy, eosinophilia (> 500 eosinophils/μL), atypical lymphocytes, elevated liver enzymes, and elevated creatinine.[3] Pneumonitis has also been associated with anticonvulsant hypersensitivity syndrome, and based on clinical presentation, it is likely that our patient had this feature.[4] If not recognized and treated, anticonvulsant hypersensitivity syndrome can progress to hepatic or renal failure, with liver failure from hepatitis as the most common cause of death.

Most cases of lamotrigine-associated anticonvulsant hypersensitivity syndrome occur in the first 8 to 12 weeks of treatment, with the onset of fever, lymphadenopathy, and cough. The diagnosis should be suspected in any patient who presents with symptoms of an upper respiratory tract infection after recently starting lamotrigine treatment. Cessation of lamotrigine is essential, and the patient should be closely monitored over the next several weeks for the development of erythema multiforme rashes and other systemic problems, such as hepatitis and renal failure, as residual symptoms can persist for weeks.[5] Intravenous steroids may also have utility in slowing the progression of the syndrome.[1] With the proper recognition of lamotrigine-associated anticonvulsant hypersensitivity syndrome, the risk of morbidity and mortality of this rare condition can be reduced.

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Case Report of Olanzapine-Associated Elevation of Serum Creatine Kinase in a 16-Year-Old Boy With Heat Stroke

Sir: A potential common linkage has been proposed among hyperthermic syndromes such as neuroleptic malignant syndrome (NMS), malignant hyperthermia, and heat stroke.[1] These 3 syndromes may be induced by different mechanisms, but all involve breakdown in the normal thermogenic mechanisms responsible for maintaining body temperature. They all cause different degrees of central nervous system changes. Other physiologic abnormalities specific to each syndrome suggest that the hyperthermia is part of a more general hypermetabolic state. Marked elevation of serum creatine kinase (CK), in the absence of classic signs and symptoms of NMS, in patients treated with atypical antipsychotics has been described in the literature.[2–7] Newer atypical antipsychotics have potent serotonin ($5\text{-}HT_2$) and weaker dopamine (D_2) receptor binding properties, which are thought to contribute to lesser occurrence of extrapyramidal symptoms or NMS as opposed to conventional antipsychotics. Olanzapine has a particularly propitious ratio of serotonin to dopamine. However, sporadic cases of NMS and isolated cases of CK elevation associated with olanzapine have been reported since the introduction of the drug in 1996. Here, we describe a case of marked reversible elevation of serum CK associated with olanzapine treatment in an adolescent boy with recent history of heat stroke.

Case report. Mr. A, a 16-year-old previously healthy boy, developed heat stroke while actively participating in a sporting camp. Initially, he was taken to a local hospital (in 2006), where he was found to be hyperthermic at 106° F and to have labile blood pressure and encephalopathy. He was intubated, rehydrated, and cooled. Computed tomography scan of the head did not reveal any abnormality. He had multi-organ failure and was transferred to our facility for further management after 6 hours.

On admission evaluation, he was afebrile, heart rate was 94 beats per minute, respiratory rate was 18 breaths per minute, and blood pressure was 140/80 mm Hg. He had bilateral subconjunctival hemorrhages, erythematous maculopapular rash, and, neurologically, had nonspecific responses to verbal stimulation. He was found to have respiratory failure, renal failure, hepatic dysfunction, and disseminated intravascular coagulation. Laboratory results at admission were as follows: sodium, 142 mEq/L; potassium, 5.4 mEq/L; blood urea nitrogen, 44 mg/dL; creatinine, 7.4 mg/dL; conjugated bilirubin, 6 mg/dL; unconjugated bilirubin, 2.4 mg/dL; aspartate transaminase, 6982 U/L; alanine transaminase, 5954 U/L; lipase, 2601 U/L; and amylase, 262 IU/L.

He was placed on continuous venovenous hemofiltration for acute renal failure secondary to severe rhabdomyolysis and was treated for liver insufficiency, disseminated intravascular coagulopathy, and metabolic disturbances. Two days after admission, he was extubated and placed on hemodialysis. Five days after admission, he remained insomnic and intermittently agitated with significant disorientation, confusion, delirium, and hallucinations. Magnetic resonance imaging of the head showed small areas of ischemia of unclear significance. Medication strategies were implemented in an effort to help the patient to reorient, sleep, and decrease his agitation. He became disinhibited when given a 1-time dose of lorazepam. Considering his agitation, visual hallucinations, and delirium, 7 days later he was started on treatment with olanzapine 2.5 mg orally, repeated twice during the night. The choice of haloperidol or other neuroleptics with higher D_2 affinity was deferred because of increasing evidence to support a link between thermodysregulation and NMS[8] and his history of extreme sympathetic nervous system activation and/or dysregulation in response to physical and psychological stress, which could couple with haloperidol's potent dopaminergic blockade and serve as a predisposing factor. Since atypical antipsychotics have lesser incidence of extrapyramidal symptoms and development of NMS than the typical neuroleptics due to their unique mechanism of action on receptor blockage, we chose to try olanzapine for his delirium and sleep problem.

Parents and staff noted improvement in the form of less agitation, better sleep, and absence of hallucination. However, laboratory results drawn the next day showed a significant elevation in CK; from 808 U/L at baseline to 2133 U/L (normal range: 35–230). Prior to administration, aspartate transaminase and alanine transaminase were 266 and 393 U/L, respectively, and conjugated bilirubin was 19.9 mg/dL. Post administration enzyme levels were 638 and 493 U/L, respectively, with a conjugated bilirubin of 17.5 mg/dL. Blood urea nitrogen and creatinine were unchanged from pretreatment levels. Because of the concerns that olanzapine may have exacerbated his hypermetabolic state and induced further rhabdomyolysis, it was immediately discontinued. The patient did not meet any criteria of NMS as per DSM-IV-TR and did not show any sign of developing muscle rigidity, temperature elevation, extrapyramidal symptoms, or new change in mental status. Creatine kinase levels further increased to 4681 U/L before beginning to drop again to normal levels over a period of 1 week. During this time, the patient did not have any type of intramuscular injections, new medications, or restraints, which could potentially cause muscle injury leading to a rise in CK levels. The patient's mental status began to improve each day. After a 23-day hospitalization, he was transferred to a facility near his home for rehabilitation. Mental status on discharge was oriented with cognitive abilities grossly intact.

Isolated marked elevation of CK associated with atypical antipsychotics, without other features of NMS, has been reported in the literature. One study found transient increases in CK in 10% of patients treated with both conventional and newer atypical antipsychotics.[9] Exact pathophysiology and clinical implications of isolated elevation in CK remain unclear. Meltzer[10] has demonstrated 5-HT–induced toxicity to skeletal muscle in rodents leading to necrosis and massive increase in CK. On the basis of this evidence, it is postulated that atypical antipsychotics could interact with endogenous 5-HT to cause some skeletal muscle injury. Dopaminergic receptor blockade is believed to be the main pathophysiology for signs and symptoms of NMS; however, some authors advocate for dysregulated sympathetic nervous system hyperactivity in cases of NMS.[8] Some authors have suggested that elevated CK may be the beginning of potential NMS, and early diagnosis and immediate discontinuation of the offending drug may prevent the fatal condition.[11]

Several diagnostic criteria for NMS are used in the literature, but the most commonly employed are the DSM-IV-TR research criteria, which define the syndrome as severe muscle rigidity and elevated temperature associated with taking neuroleptics and, in addition, having 2 of the following: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leucocytosis, and laboratory evidence of muscle injury. However, our patient did not show any features of full blown NMS. In the literature, there is increasing evidence[12] to support a link between several hyperthermic syndromes, including NMS and serotonin syndrome. Both involve a breakdown in the normal thermogenic mechanisms responsible for maintaining body temperature. The hypothalamus and sympathetic nervous systems are primarily involved and are regulated by levels of serotonin, dopamine, and norepinephrine. It has been suggested that some patients could be more vulnerable to medication-induced hyperthermic syndromes. For example, elevated body temperature has been associated with increased toxicity of the serotonergic agent 3,4-methylenedioxymethamphetamine (MDMA) in studies looking at causes of serotonin syndrome.[12] It does not seem unreasonable to hypothesize that an elevated or dysregulated body temperature would also make a patient more susceptible to the effects of neuroleptic medication and may even increase the risk of NMS. Our patient had recently been treated for heat stroke, a break down of the body's ability to dissipate heat. This may have made him more vulnerable to the effects of neuroleptic medication on the hypothalamus and sympathetic nervous system. At the time of administration, the potential benefits of olanzapine far exceeded the risk of developing complications. However, careful monitoring of liver function and CK levels was required.

One should be aware of the fact that atypical neuroleptics, the use of which is becoming increasingly common in inpatient and outpatient settings, can cause complete or partial NMS-like presentation or an isolated increase in CK, which could herald the onset of full blown NMS. Great care should be taken in treating delirium with atypical antipsychotics in a patient with a history of heat stroke. Awareness of a triad of heat stroke, malignant hyperthermia, and NMS should always be kept in mind. Baseline pretreatment CK levels and frequent monitoring during the treatment period could avoid this potentially dangerous syndrome. Further research is warranted to investigate the precise pathophysiology and clinical implications of isolated CK elevation and to identify patients who are at higher risk of developing complications from neuroleptic medications.

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

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Improvement in Depressive Symptoms With Felbamate: A Case Report

Sir: Prevalences of psychiatric illness are significantly higher in patients with seizure disorder, essentially with temporal lobe and refractory epilepsy, with depression occurring in up to 30%.[1] Felbamate is an antiepileptic drug used as both monotherapy and adjunctive therapy in patients with partial seizures with or without secondary generalization. There are sparse data concerning the effects of felbamate in psychiatric disorders. To our knowledge, this is the first case reporting antidepressant effects of felbamate.

Case report. Ms. A is a 29-year-old woman who has intractable seizures. When she was 16 years old, she had Epstein-Barr virus encephalitis and was in a coma for about 3 weeks. She has had seizures since then with a frequency of once per week, has undergone extensive workup by neurologists on several occasions, and has been diagnosed with both grand mal and petit mal seizures. The duration of her grand mal seizures range from 10 to 15 minutes. There is no history of head trauma or febrile seizures. Magnetic resonance imaging of her head revealed bilateral mesial temporal lobe sclerosis. Her recent electroencephalogram showed a generalized slowing maximal in the posterior regions with broadly contoured slow spike and wave discharges with less frequent temporal epileptiform discharges. Over the course of her seizures, she has tried several antiepileptic medications in different combinations with minimal benefits; these include carbamazepine, topiramate, oxcarbazepine, lamotrigine, divalproex sodium, phenobarbital, zonisamide, primidone, levetiracetam, pregabalin, clonazepam, phenytoin, gabapentin, and felbamate. Other options are being explored, such as vagal nerve stimulation and epilepsy surgery.

She has a family psychiatric history of depression in her mother. There is no substance use history. In 2007, the patient reported an interesting finding of a significant improvement in her mood with felbamate. Over the course of her illness, she has been on treatment with felbamate on 3 different occasions and has observed that her mood is good when she is taking felbamate. She has also noticed an improvement in energy levels and describes that she is less tearful and has an overall sense of well-being whenever she is on treatment with felbamate. Her most recent dose of felbamate was 600 mg 3 times a day, and the neurologists were planning to discontinue this due to the concerns of adverse effects. This patient was worried about having a relapse of depression when her felbamate was discontinued. We offered her a trial of sertraline, and she was willing to try.

Disruption of glutamate neurotransmission has been linked to major depression, and drugs targeting N-methyl-D-aspartate (NMDA) receptors have shown antidepressant properties.[2]

Some animal studies have shown that many antidepressants have activity on the NMDA receptors. One of the proposed mechanisms of action of fluoxetine is by suppressing glutamate release.[3] Felbamate indirectly antagonizes NMDA receptors.

A better control of seizures leads to symptomatic improvement in comorbid depression. In our patient, felbamate was not very effective in improving her seizures, but symptomatic improvement in her depression was evident with its use. It has been suggested that a better psychiatric outcome in patients with seizure disorder could be achieved by treating baseline "anergic" profiles (apathy, depression, fatigue) with activating antiglutamatergic drugs such as lamotrigine and felbamate.[4] However, felbamate's adverse effect profile, with black box warnings of risks such as aplastic anemia and fatal hepatitis, may limit its use. Additional research with controlled studies is warranted to substantiate our finding of an antidepressant effect of felbamate.

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

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Small Doses of Aripiprazole Augmentation of Antidepressant Treatment: A Report of 3 Cases

Sir: Several studies showed the usefulness of aripiprazole augmentation of antidepressant treatment in refractory depression.[1–4] Berman et al.[4] suggest that the effective dose for many (depressed) patients is lower than those recommended for schizophrenia and bipolar disorder and that the true efficacious

dose for some depressed patients may have been even lower. In most cases, however, aripiprazole was started at 5 to 10 mg/day and increased to 10 to 30 mg/day.[1–3] A smaller dose may be useful to prevent side effects and thereby reduce the likelihood of patient dropout. There is, to my knowledge, no report describing small doses of aripiprazole augmentation and maintenance in the treatment of depressed patients.

I report 3 cases of refractory depression responding to 3 mg/day of aripiprazole that were maintained in remission with the same dose. This study was approved by the Oita University Faculty of Medicine ethics committee, and written informed consent was obtained from the 3 patients.

Case 1. Ms. A, a 61-year-old woman, had DSM-IV major depressive disorder of 2 years' duration. Just before the start of aripiprazole augmentation in 2006, she was receiving 150 mg/day of fluvoxamine for 2 months, and her Hamilton Rating Scale for Depression (HAM-D)[5] score was 19. Twelve days after aripiprazole 3 mg/day was added to her fluvoxamine regimen, her HAM-D score improved to 6. After 5 months of remission, she complained of insomnia, and aripiprazole was discontinued whereas fluvoxamine was continued. Within 2 weeks, she experienced relapse of depression, and aripiprazole was resumed. Two weeks later, her condition improved, and subsequently her depression was in remission for 5 months.

Case 2. Mr. B, a 46-year-old man, had DSM-IV major depressive disorder of 7 years' duration. Just before the start of aripiprazole augmentation in 2006, he had been receiving the combination of 150 mg/day of amoxapine, 100 mg/day of sertraline, 50 mg/day of trazodone, and 30 mg/day of mianserin for 7 weeks, and his HAM-D score was 14. Two weeks after 3 mg/day of aripiprazole was added to this regimen, his HAM-D score improved to 5. After 6 months of remission, he was restored to his position as a junior high school teacher. During another 6 months on treatment with this regimen, he gradually adjusted to his job.

Case 3. Ms. C, a 27-year-old woman, had DSM-IV major depressive disorder of 3 years' duration. Just before the start of aripiprazole augmentation in 2006, she had been receiving the combination of 40 mg/day of paroxetine, 100 mg/day of maprotiline, and 800 mg/day of lithium for 4 weeks, and her HAM-D score was 21. One week after 3 mg/day of aripiprazole was added to this regimen, her HAM-D score dramatically improved to 0. Thereafter, lithium and paroxetine were discontinued without relapse. After 5 months of remission, she began to work as a clerk. During another 5 months, she gradually adjusted to her job while undergoing treatment with 100 mg/day of maprotiline and 3 mg/day of aripiprazole.

These patients responded very well to 3 mg/day of aripiprazole augmentation, and the effects were maintained for several months without increasing the aripiprazole dosage. Particularly in case 1, aripiprazole withdrawal induced relapse and resumption led to a return of remission. Although placebo effects cannot be ruled out completely, these findings suggest that small doses of aripiprazole addition may be useful for some patients with refractory depression. Further controlled trials are required to draw a definite conclusion.

Dr. Terao reports no financial affiliation or other relationship relevant to the subject of this letter.

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Transdermal Nicotine in Adult ADHD With Depression and Anxiety

Sir: Focusing and memory ability are dysfunctional in attention-deficit/hyperactivity disorder (ADHD),[1] which commonly co-occurs with depression and anxiety.[2] Treatment with methylphenidate or amphetamine frequently corrects inattentiveness and memory impairment, but is less reliable in the alleviation of the accompanying depression and anxiety. These medicines have depression and anxiety as reported side effects. In addition to the involvement of dopaminergic and noradrenergic neurons, there is evidence to suggest that cholinergic neurons are involved in the biobehavior associated with ADHD.[3]

Nicotine-dependent individuals experience more inattentiveness, forgetfulness, depression, and anxiety during withdrawal, and nicotine replacement is thought to reverse withdrawal-induced focusing and memory impairment,[4] depression,[5] and anxiety.[6] Changes in focus and memory ability, associated with nicotine dependence and replacement treatment, are directly mediated by nicotinic-cholinergic neurons, and depression and anxiety are thought to be indirectly mediated by pathways between nicotinic-cholinergic receptors and dopaminergic, noradrenergic, serotonergic, and gabaminergic neurons.[7]

The following report illustrates a case of adult ADHD associated with depression and anxiety that responded to transdermal nicotine patches.

Case report. Mr. A, a 43-year-old white man, was self-referred in June 2006 for an ADHD evaluation. Although he had symptoms of depression and anxiety, he only fulfilled DSM-IV-TR criteria for ADHD. Mr. A had been taking metoprolol (50 mg daily) for mild hypertension for several years, and after evaluation in our facility in 2006, he began medication trials with amphetamine mixed salts (10 mg 3 times daily), methylphenidate (36 mg), and bupropion (150 mg). He experienced marked irritability; each stimulant needed to be discontinued within a couple of days, and the bupropion was stopped within 3 weeks of starting. Mr. A then began a trial using the 7 mg transdermal nicotine patch from 7 a.m. until 4 p.m. on Monday through Friday, and on weekends as needed. He developed mild chest discomfort at around noon of the first treatment day. Mr. A was instructed to remove the patch and begin again the following morning using the equivalent of a 3.5 mg transdermal patch. This was crafted by partially peeling the foil backing and cutting

the foil in half with scissors, being certain not to cut or disturb the patch's delivery system in any way. (Caution: the manufacturer does not endorse this technique, and dosing may be inconsistent from day-to-day.) In this way, Mr. A applied a half-exposed 7 mg patch—about 3.5 mg—from 7 a.m. until 4 p.m. on alternate mornings. A fully exposed patch was to be applied on the following day. Mr. A's ADHD symptoms, which mainly consisted of inattentiveness and poor reading comprehension, completely resolved within an hour of starting approximately 3.5 mg of nicotine from the transdermal patch, as did his depressive and anxious symptoms. Problems with inattentiveness, reading comprehension, depression, and anxiety partially returned (about 30%) after the patch was removed each day. He continued to respond for about 1 year as long as the patch was applied, without the need to increase the transdermal dose. His blood pressure remained stable throughout, and although Mr. A is a recovering cigarette smoker with over 10 years clean, use of the transdermal patch has not led to cigarette relapse. He continues to report fewer thoughts and cravings to pick up "just one" cigarette as compared to his prepatch thought and craving frequency.

This case report neither rules out the placebo effect, nor does it prove that transdermal nicotine is useful in managing adult ADHD with depression and anxiety. However, it does suggest that the beneficial effect of transdermal nicotine may be attributed to biobehavioral pathways common to chronic nicotine withdrawal and ADHD with depression and anxiety. Nicotine agonists and delivery systems may be new treatments for adult ADHD. Larger well-designed studies are warranted to evaluate the therapeutic potential of nicotine delivery systems in otherwise medically stable adults with ADHD accompanied by depression and anxiety. Further exploration of the nicotinic-cholinergic system may also expand our understanding of the neuropsychiatry underlying ADHD.

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

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Case Report of Oculogyric Crisis With Ziprasidone in a Minor

Sir: The following case report describes the occurrence of oculogyric crisis in a 14-year-old female patient prescribed ziprasidone on an inpatient unit.

Case report. Ms. A, a 14-year-old female, was hospitalized psychiatrically in April of 2006 due to suicidal thoughts and self-abusive behaviors. Ms. A had superficial lacerations on her left wrist and had reported significant mood changes. She had been in outpatient treatment without medication experiencing significant mood changes. She was diagnosed with bipolar disorder not otherwise specified. Her psychiatric history revealed 3 prior psychiatric admissions, first in March 2005 and subsequently in April and August of 2005, also for suicidal thoughts. She also had a history of sexual abuse. Her family psychiatric history revealed a grandmother with mental illness, her mother's cousin had completed suicide, and her father had alcoholism. Her medical history and laboratory tests were unremarkable. There were no drug or alcohol issues.

On mental status examination, Ms. A appeared to be a well-developed and well-nourished adolescent who looked her stated age. She was alert and oriented to time, place, and person. She was cooperative and made good eye contact. Her speech was coherent with normal rate and rhythm. Her thought processes were logical and sequential, with no flight of ideas, looseness of association, thought withdrawal, or thought insertion present. Her cognitive functions were intact.

Ms. A was initially started on treatment with duloxetine 30 mg daily, which was discontinued after 4 days, and then ziprasidone 40 mg daily was started for mood stabilization. After 2 doses of ziprasidone, she experienced painful arching of the neck and upward rolling of the eyes with breathing difficulty, all of which were relieved by 2 injections of intramuscular benztropine 30 minutes apart. The ziprasidone was discontinued. The oculogyric crisis developed a couple of hours after the second dose of ziprasidone and resolved approximately 1 hour after the second injection of benztropine. Ms. A was discharged the next day without medications, having no thought of harming herself and having clear and goal-directed thinking, and the oculogyric crisis and dystonic reaction had completely resolved.

The above symptoms were characteristic of an oculogyric crisis, which is a specific type of dystonic reaction. The prescription of ziprasidone in children is off-label as it has not been approved by the U.S. Food and Drug Administration for children for the treatment of bipolar disorder. Although atypical antipsychotics are less likely to cause extrapyramidal symptoms (EPS), ziprasidone is associated with dose-related EPS.[1] There is 1 previous case report of oculogyric crisis in a minor with ziprasidone. Ramos et al.[2] report an acute dystonic reaction with an oculogyric crisis in an 11-year-old boy with pervasive developmental disorder not otherwise specified, mild mental retardation, tics, and psychotic symptoms. All of the medications he had been taking were discontinued prior to being prescribed 40 mg of ziprasidone a day. The boy experienced oculogyric crisis after 6 weeks of taking ziprasidone; the reaction completely subsided after 24 hours of being given diphenhydramine. In our patient, the symptoms started after only 2 doses of ziprasidone were administered.

Oculogyric crisis has also been reported with olanzapine as well as clozapine, both of which are atypical antipsychotics; this class is known to have a low propensity to cause EPS.[3,4] As

the atypical antipsychotic agents are being increasingly used by nonpsychiatrists in primary care, clinicians should be familiar with this side effect and alert to early detection and rapid initiation of treatment.

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Hyperosmolar Hyperglycemic State in a Patient Taking Risperidone

Sir: The association of neuroleptics with metabolic disturbances has been well described.[1] Several reports have associated atypical antipsychotics with hyperosmolar hyperglycemic state (HHS); however, most cases have involved olanzapine.[2,3] This letter reports a case of HHS associated with risperidone use.

Case report. Mr. A, a 39-year-old man with Asperger disorder, presented to the emergency department in August 2007 complaining of a 1-day history of general malaise, vomiting, polyuria, and polydipsia. His medical history included hypertension, hypercholesterolemia, and a seizure disorder treated with carbamazepine. His other medications included hydrochlorothiazide, ranitidine, and atenolol.

Three years prior to admission, Mr. A was diagnosed with schizophrenia-like psychosis of epilepsy. His carbamazepine dose was increased to 600 mg/day, and he was started on treatment with 4 mg/day of risperidone. At the time, he weighed 102 kg and had not been diagnosed with diabetes. Over the next 10 months, his weight increased to 122 kg. He displayed neither seizure activity nor return of psychosis; however, he did complain of depressed mood. He was started on treatment with 10 mg/day of paroxetine, which relieved some symptoms. His weight increased to 135 kg over 12 weeks.

On examination at the time of the current presentation, Mr. A displayed tachycardia, globally decreased cognitive ability, and intermittent left upper extremity clonus. Laboratory evaluation revealed a serum glucose level of 1179 mg/dL, a creatinine level of 2.7 mg/dL, a blood urea nitrogen level of 42 mg/dL, a potassium level of 4.0 mmol/L, and an anion gap of 22 mEq/L. The patient's blood osmolality was elevated at 378 mOsm/kg water. His carbamazepine level was therapeutic at 6.0 μg/mL. His glycosylated hemoglobin (HbA_{1c}) level was 14.6%. His cholesterol, triglycerides, and low-density lipoprotein levels were all elevated. Electroencephalogram revealed generalized slowing, and results of computed tomography of the head were within normal limits. Mr. A showed no evidence of infection. He was admitted to the medical intensive care unit for treatment of HHS.

Fluid and electrolyte management, 2 important therapies in HHS treatment, were applied. Regarding the psychotropics, treatment with risperidone was discontinued, paroxetine was tapered, and an appointment was scheduled for outpatient psychiatric care. Mr. A was also discharged with subcutaneous insulin treatment.

This patient experienced a severe alteration in metabolic parameters while taking an atypical antipsychotic. His weight increased with use of risperidone, and then increased at a faster rate with the coadministration of paroxetine. While this patient was obese prior to risperidone therapy, he carried no diagnosis of type 2 diabetes mellitus until this admission. A recent review of schizophrenic patients treated with atypical antipsychotics diagnosed with diabetes presenting as diabetic ketoacidosis revealed only 1 case associated with risperidone use.[4] The patient's HbA_{1c} level of 14.6% implies that he had elevated glucose levels, and undiagnosed type 2 diabetes mellitus, for at least several weeks prior to admission. This patient's risk factors for type 2 diabetes mellitus included obesity, hypertension, dyslipidemia, and neuroleptic therapy.

It is appropriate to perform diabetes screening for at-risk patients receiving neuroleptic therapy.[5] This case demonstrates the metabolic syndrome presenting as HHS in a patient taking risperidone.

Mr. Cerimele reports no financial or other relationship relevant to the subject of this letter.

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