

# Letters to the Editor

## Thiazide Diuretics and Lithium Levels

**Sir:** Although Dr. Dunner's recent contribution to the *Journal*<sup>1</sup> was most useful, I hasten to point out an obvious error.<sup>1</sup> On page 79, the article asserts: "The use of thiazide diuretics is the equivalent of *lowering* [italics mine] the lithium dose." The reference provided,<sup>2</sup> of course, states just the opposite.

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**Editor's Clarification:** When a thiazide diuretic is added to a lithium regimen, the lithium level usually rises. With the addition of thiazide, therefore, one can achieve the same lithium level at a lower dose of lithium.

—A.J.G.

## Lithium Therapy for Corticosteroid-Induced Mood Disorder

**Sir:** I read with interest the article by Wada et al.,<sup>1</sup> which investigated clinical characteristics and treatment of 9 cases of corticosteroid-induced mood disorder. I would like to comment on their pharmacotherapy as follows.

First, Wada et al.<sup>1</sup> claimed that lithium should be carefully avoided because quite a few diseases treated with corticosteroids, such as nephrotic syndromes or systemic lupus erythematosus (SLE), provoke renal dysfunction. I cannot agree with their claim: I have treated 4 cases of steroid-induced depression in which lithium was remarkably effective and no severe side effects occurred.<sup>2,3</sup> One of the patients suffered from depression induced by steroid and from moderate renal dysfunction due to SLE. When 600 mg/day of lithium was started, her depression improved greatly. However, serum lithium levels increased from 0.4 to 0.8 mEq/L within 1 week, and lithium treatment led to the exacerbation of a finger tremor. Lithium was then discontinued, although it had been dramatically effective. Thereafter, the patient's depression was exacerbated, and she was put on 400 mg/day of lithium. At the start of treatment, serum lithium levels were less than or equal to 0.4 mEq/L and did not increase further. The low dose and low levels of lithium brought about a dramatic improvement again and were associated with only a fine finger tremor. Although my experience may be anecdotal and needs to be confirmed by further studies, lithium is not always contraindicated in patients with renal dysfunction. Of

course, it is necessary to measure serum lithium levels and titrate lithium doses frequently in such a situation. Also, our equation to predict daily lithium dose<sup>4</sup> may be helpful because it includes a variable of renal function.

Secondly, a similar situation occurred in case 1 reported by Wada et al. In that patient, lithium was avoided because of hypothyroidism.<sup>1</sup> However, lithium can be used in hypothyroidism if thyroid hormones such as thyroxine are added to lithium therapy to maintain thyroid function. In hindsight, because carbamazepine could not be continued owing to an urticarial rash and because the patient unfortunately committed suicide, they should have tried lithium in combination with thyroxine. This combination might have been helpful for the patient.

In conclusion, I believe that lithium should be carefully *used* in corticosteroid-induced mood disorder, in contrast to the claim by Wada et al. that lithium should be carefully *avoided*.

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## Wada and Colleagues Reply

**Sir:** We appreciate the comments on our article<sup>1</sup> by Dr. Terao and would like to respond to several issues he has raised. He concluded that lithium should be used carefully for patients with corticosteroid-induced mood disorder, even if renal dysfunction or hypothyroidism coexists. We do not regard lithium as first-line treatment for patients with significant renal disease, in accordance with the warning clearly stated in the prescribing information for lithium. Carbamazepine and valproate showed substantial effectiveness for corticosteroid-induced mania in our series. We have been presented with 2 additional single-episode cases of corticosteroid-induced hypomania in which patients were effectively treated with valproate (unpublished data, 1999). Carbamazepine and valproate have proven effectiveness comparable to that of lithium for patients with primary mania.<sup>2,3</sup> Although we do not consider lithium to be absolutely contraindicated for patients with renal disease, carbamazepine or valproate should be a first-line treatment. If neither carba-

mazepine nor valproate is effective, lithium treatment may be undertaken with extreme caution, including daily serum lithium determinations and dose titration. Antipsychotics are another treatment option for corticosteroid-induced mania.

Previously existing hypothyroidism, as was found in case 1 of our report, does not necessarily constitute a contraindication to lithium treatment. However, depression in case 1 was severe and developed a fluctuating course, which was predictive for poor response to lithium. Valproate rather than lithium should have been tried in advance for the patient. Unfortunately, in 1990, when the patient was admitted, valproate was not generally accepted as a beneficial mood stabilizer in Japan.

Dr. Terao recommended lithium use for corticosteroid-induced depression from his clinical experience of 4 anecdotal cases. Our report<sup>1</sup> included 6 patients with corticosteroid-induced depression who were effectively treated with antidepressants, including tricyclics. Intravenous clomipramine was obviously effective for 2 patients whose condition had deteriorated into depressive stupor.<sup>1</sup> Therefore, we recommend antidepressant medication as a first-line treatment for corticosteroid-induced depression. This treatment regimen remains an issue of some dispute and requires further investigation. Concomitant use of mood stabilizers is desirable in recurrent cases, since these patients clinically present with bipolar disorder.

In conclusion, effective psychopharmacologic treatment options for corticosteroid-induced mood disorder have to be explored when indicated, with consideration being given to the underlying diseases.

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### Chilaiditi Syndrome–Associated Schizophrenia: 3 Case Reports

**Sir:** Hepatodiaphragmatic interposition of the colon is an uncommon, usually asymptomatic, and typically incidental radiographic finding. In 1910, Viennese radiologist Demetrius Chilaiditi described 3 clinical cases with radiographic findings; the syndrome now bears his name.<sup>1</sup> The majority of these patients are without symptoms; however, abdominal pain, distention, vomiting, anorexia, and constipation are known clinical presentations of Chilaiditi syndrome.<sup>1</sup> Although it was suggested that this condition has a higher rate of incidence in patients hospitalized for psychosis and mentally retarded patients than in other individuals,<sup>2–4</sup> there has been only 1 authoritative article to promote the knowledge of this syndrome in the domain of psychiatry.<sup>5</sup> Here, we report 3 schizophrenic patients whose radio-

graphs showed the signs of this syndrome, and we discuss the clinical significance of this syndrome in psychiatry.

**Case 1.** Mr. A, a 61-year-old single man, had experienced insomnia and auditory hallucinations and was diagnosed with schizophrenia when he was 20 years of age. Since then, he has had 5 psychiatric hospitalizations. During the last, he had been hospitalized for 4 years when his condition deteriorated and he became autistic. He was given 200 mg/day of sulpiride, 10 mg/day of haloperidol, 12 mg/day of nemonapride, and 2 mg/day of risperidone for his psychosis. Routine laboratory examination results were within the normal limits for blood, urine, and feces. His intestinal duct was filled with gas, and his abdomen was expanded (i.e., meteorism). When he was 60 years of age, a chest radiograph showed an accumulation of gas between the liver and diaphragm. The interposed organ was considered to be the colon because of the presence of haustrations within the gas. He had no subjective symptoms except for constipation. He was given 22.5 mg/day of sodium picosulfate, and several enemas were administered. Soon after, the gas of the colon gradually descended, but it was usually located in front of the liver. Antipsychotic drugs were continually given to him during this episode.

**Case 2.** Mr. B, a 61-year-old single man, had complained of delusions of reference at 18 years of age. His illness was diagnosed as schizophrenia, and he was admitted to a psychiatric hospital at 19 years of age. Since then, he has required continuous hospitalization for 42 years because of severe symptoms of incoherence, delusions, and psychomotor excitement. At the age of 58, he had meteorism and a high fever. A physical examination showed no abnormality of the chest, but the abdomen was apparently enlarged and tympanic. A radiograph of the chest showed a mass of gas in the colon with haustrations between the liver and diaphragm. A radiograph of the abdomen revealed an abundance of gas, but no niveau was detected. Mr. B had chronic constipation, but he did not complain of any subjective symptom (e.g., abdominal pain). Antipsychotic drugs (perphenazine, 56 mg/day; bromperidol, 18 mg/day; zotepine, 75 mg/day; and chlorpromazine, 150 mg/day) were discontinued, and he was given 37.5 mg/day of sodium picosulfate. Enemas were frequently administered. After 2 weeks, meteorism was relieved, and the gas between the liver and diaphragm had disappeared.

**Case 3.** Ms. C, a 59-year-old single woman, had delusions of reference, insomnia, and psychomotor excitement at 20 years of age. Her illness was diagnosed as schizophrenia. She was admitted to a psychiatric hospital at the age of 20, where she has since remained. Pharmacologic therapy (bromperidol, 15 mg/day; sulpiride, 150 mg/day; methotrimeprazine, 200 mg/day; risperidone, 5 mg/day) was administered, but her condition gradually deteriorated. At the age of 54, Ms. C was rather depressed. She had constipation, poor appetite, and a dull pain in the right upper region of the abdomen. The abdomen had a gurgling and tympanic sound. Results of routine laboratory analyses of the blood and urine were all within normal limits. A radiograph of her chest showed gas in the colon with haustrations between the liver and diaphragm and also revealed that the colon below the left diaphragm was filled with gas. The antipsychotic drugs were discontinued, and Ms. C was instead given digestive and laxative drugs. Her constipation and pain were relieved within a week; however, the gas between the liver and diaphragm still remained, as determined by her chest radiograph.

Chilaiditi syndrome is reported in 0.003% to 0.025% of the radiographs in mass radiographic screenings of the chest.<sup>3,6</sup> On the other hand, the incidence of this syndrome in psychosis and mental retardation in hospitals is reported to be 0.147% to 1.000%.<sup>2–4</sup> This syndrome apparently occurs more often in

patients of mental hospitals than in other individuals. The etiology of this interposition has been discussed in most of the published research on the subject. Choussat and Choussat-Clausse<sup>7</sup> analyzed and listed the causes of this syndrome as follows: (1) hepatic factors: ptosis of the liver, a small liver, relaxation of the suspensory ligament and fixation of the liver by adhesions associated with traction produced by the gastrohepatic ligament or perigastritis; (2) diaphragmatic factors: abnormally high diaphragm due to degeneration or thinning of the diaphragmatic musculature, injury or disease of the phrenic nerve causing paralysis of the diaphragm, changes in intrathoracic pressure as in cases of, for example, tuberculosis or emphysema; (3) intestinal factors: megacolon or abnormal accumulation of gas in the colon causing an upward displacement of the diaphragm, abnormal mobility of the colon of congenital origin. In general, a combination of factors may be active in the development of this condition.

The high rate of incidence of the interposition in psychotic individuals and patients with mental retardation may be due to a tendency toward constipation and meteorism. Torgersen<sup>3</sup> suggested that the meteorism was due to an insufficiency of a particular cerebral cortical function. All of the patients reported here had constipation and meteorism. Recently, the "neurodevelopmental hypothesis" of schizophrenia was proposed, and abnormalities in cortical development were reported in schizophrenic patients.<sup>8,9</sup> Thus, neurodevelopmental abnormalities potentially relate to the causes of interposition. Antipsychotic drugs probably play an important role in the high rate of incidence of this syndrome in schizophrenic patients. It is well known that abnormalities in the function of the intestines such as constipation or ileus can be caused by the anticholinergic side effects of antipsychotic drugs. In all of our cases, it is obvious that Chilaiditi syndrome occurred in relation to the administration of antipsychotic drugs. Moreover, all of our patients were administered more than 2 antipsychotics. The negative symptoms in schizophrenic patients are also considered to bring about abnormalities of intestinal function and to promote the frequency of this condition. All of our patients showed profound negative symptoms such as autism and lowered spontaneity during their long hospitalization. The occurrence of this syndrome can probably be prevented if occupational therapy or recreational therapy is actively used during extended periods of hospitalization.

Chilaiditi syndrome can be either transient or permanent and is asymptomatic in almost all cases. Psychiatrists should be aware of this condition in patients' chest radiographs, because it can develop into more serious conditions such as ileus and the rate of incidence of this condition in psychotic individuals and patients with mental retardation is higher than in other individuals. Further studies are necessary to elucidate factors associated with Chilaiditi syndrome in psychiatric inpatients.

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#### Pharmacologic Treatment of Patients Hospitalized With the Diagnosis of Schizoaffective Disorder

**Sir:** We read with great interest the article by McElroy et al.<sup>1</sup> in which they provide an overview of the treatment of schizoaffective disorder. Their review of existing studies of traditional and novel pharmacologic agents resulted in a conclusion that the safety, side effect profile, and apparent thymoleptic properties of atypical antipsychotics suggested use of these agents as first-line treatment of patients with schizoaffective disorder.

We are in the process of analyzing data on the treatment of 70 patients hospitalized with schizoaffective disorder during a 6-year period from 1993 to 1999. Preliminary data from our study support the notion that psychiatrists are turning increasingly to atypical agents in the treatment of schizoaffective disorder. Our data also indicate potential utility for these agents, since patients with schizoaffective disorder appear to receive thymoleptic agents whether or not they present with prominent mood symptoms.

In a year-by-year, linear-by-linear examination over the course of the study, a statistically significant shift was found from typical to atypical antipsychotic medications ( $p < .00005$ ). In addition, lithium was used most frequently as an antimanic medication early in the study; divalproex sodium was used more frequently than lithium in the later period of the study. The trend to use divalproex instead of lithium approached statistical significance ( $p = .053$ ).

Sixty-six patients (94%) presented with active psychosis. Fifteen patients (21%) endorsed no significant mood symptoms on admission. Of the 30 patients treated with typical antipsychotic medication, 26 (87%) were also treated with a thymoleptic (antimanic or antidepressant) medication. Of the 37 patients treated with atypical antipsychotic medications, 33 (89%) were treated with a thymoleptic medication. Of the 15 patients who presented without mood symptoms, 12 (80%) were discharged on treatment with a thymoleptic medication.

Our study was naturalistic by design. Our findings indicate that, in clinical practice, patients who are hospitalized with schizoaffective disorder are treated with antidepressant or antimanic agents on the basis of the history of prior mood symptoms, regardless of whether mood symptoms are evident on admission. If the atypical antipsychotic medications prove to have significant thymoleptic effects in this population, their use may simplify pharmacologic management.



The data presented in this letter were obtained under Walter Reed Army Medical Center Protocol WU #72003E-99.

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**Inositol in the Treatment of Trichotillomania and Compulsive Skin Picking**

**Sir:** Medication treatments for trichotillomania and skin picking are less well defined than those for obsessive-compulsive disorder (OCD).<sup>1-3</sup> Although in trichotillomania, neurobiological investigation has found evidence of serotonergic dysregulation similar to that in OCD,<sup>3</sup> anecdotal reports and results of controlled trials of serotonin reuptake inhibitors (SRIs) in the treatment of trichotillomania and skin picking have not always demonstrated efficacy.<sup>4-6</sup>

Inositol, a simple isomer of glucose, is an important dietary and cellular constituent and a key precursor in the phosphatidylinositol second-messenger cycle. Although inositol has long been used as a natural remedy for anxiety and depression, its effects first received systematic evaluation in 2 separate double-blind controlled trials which showed that daily administration of 12 g of inositol over 4 weeks had antidepressant<sup>7</sup> and antipanic<sup>8</sup> effects. Inositol was subsequently found to significantly reduce symptoms in OCD patients,<sup>9</sup> although its efficacy as an augmentation strategy in treatment-refractory OCD patients is questionable.<sup>10</sup> To date, however, little research has been done on inositol in putative obsessive-compulsive spectrum disorders.

Although the mechanism of action of inositol in anxiety and depression is not clear, it might be suggested that some patients with OCD and OCD-related behaviors (such as hair pulling and compulsive skin picking) have a relative deficiency of brain inositol that may be reversed by supplementation with dietary inositol. Considering, too, that important subtypes of serotonergic and noradrenergic receptors use the phosphatidylinositol cycle as their second messenger, another mechanism of action of inositol might be through its attenuation of serotonin-2 receptor desensitization.<sup>11</sup>

We report on the possible benefits of inositol in 3 cases: as a primary treatment for trichotillomania in 1 case and as an augmentation of an SRI for compulsive skin picking in 2 cases. Inositol was administered in white powder form, in a daily dose of 18 g (6 g dissolved in water or juice, 3 times a day). None of the 3 patients reported received concurrent behavior therapy or other psychotherapeutic intervention. This is, to our knowledge, the first report on inositol as a treatment for trichotillomania and skin picking.

**Case 1.** Ms. A, a 43-year-old married woman who worked as a school secretary, presented with compulsive skin picking (face), which began when she was 17 years old. Ms. A picked her skin daily, resulting in scarring and scab formation, and she engaged in repetitive "mirror checking." She reported a pattern of premenstrual exacerbation of skin picking. Ms. A

consulted several dermatologists, who confirmed no underlying dermatologic disorder. Over the years, she was prescribed various topical creams and/or ointments, and she also attempted to camouflage the damage with makeup. She met DSM-IV criteria for body dysmorphic disorder. On psychiatric interview, Ms. A did not appear to have other self-injurious behaviors or OCD symptoms. She described mild depressive symptoms that met criteria for an additional DSM-IV diagnosis of major depression.

Ms. A was treated with citalopram (20 mg/day), but after 4 weeks, she reported no improvement. Citalopram was increased to 40 mg/day. After 6 weeks on this dose, she experienced noticeable improvement in mood, but not in skin-picking behavior. In addition, she complained of a decrease in libido on citalopram treatment, and she was unwilling that the dose be increased further. Inositol (18 g/day) was then started in addition to the citalopram (40 mg/day). Side effects experienced included flatulence and diarrhea, but these remitted in the first week. After 4 weeks of inositol augmentation, there was noticeable improvement in skin picking. From picking for hours every day and avoiding social activity, Ms. A progressed to picking her skin only once or twice a week (10 minutes at a time). Mirror-checking behavior lessened, and she also began socializing again. Her libido returned, and there was a further improvement in mood. This response was sustained at 8 weeks of treatment. At week 8, she was clinically assessed to be "very much improved" (Clinical Global Impressions-Improvement scale [CGI-I] score of 1).<sup>12</sup>

**Case 2.** Ms. B, a 21-year-old single woman employed as a massage therapist, was seen for evaluation of chronic, repeated hair pulling (scalp, pubic, and leg hair), which began when she was 12 years old. Her hair pulling had become worse in the previous 2 years. She used tweezers to pull out ingrown pubic and leg hair. She developed bald patches on her scalp and had begun wearing a hat or a wig in public at all times. She had never ingested her hair. Ms. B had not responded to a course of paroxetine (20-40 mg daily for 6 months) 5 years previously.

On psychiatric evaluation, Ms. B reported that she usually pulled out her hair in a "focused" rather than an "automatic" way, and this typically occurred at home. She described mounting tension before hair pulling, followed by feelings of relief after pulling out her hair. She met DSM-IV criteria for trichotillomania. Ms. B also had moderate depressive symptoms at the initial interview and fulfilled DSM-IV criteria for a major depressive episode.

Ms. B was prescribed inositol (18 g/day). She experienced mild abdominal bloating, which resolved on day 10 of treatment. After 4 weeks on inositol treatment, she reported that her hair pulling was much reduced (from pulling hair daily, she was now pulling once a week). At week 4, she was rated clinically as "much improved" (CGI-I score of 2).<sup>12</sup> Her productivity at work and her low mood also improved. After 12 weeks on inositol treatment, she continued to make good progress.

**Case 3.** Ms. C, a 26-year-old single woman employed as a public relations consultant, had a history of hair pulling (scalp and pubic hair) for 10 years and compulsive nail biting since childhood. Recently, her hair pulling had started to interfere with her work (she was devoting about an hour of work time per day to pulling) and was drawing comments from her colleagues. On assessment, Ms. C fulfilled DSM-IV criteria for trichotillomania, but did not present with comorbid depressive or anxiety symptoms. She had received no previous treatment, and she was unwilling to take medication or be referred for therapy. She did agree to treatment with inositol (18 g/day). She complained of mild side effects with inositol (headaches and abdominal cramps) that persisted for 3 to 4 weeks. There was, however, a

considerable reduction in both hair pulling and nail biting at week 8 of treatment, and Ms. C was rated as "much improved" (CGI-I score of 2).<sup>12</sup> Improvement persisted at follow-up 8 weeks later.

We report here on 3 cases in which inositol, a glucose isomer with notable effects on serotonin, was useful as primary treatment in 2 patients unwilling to take SRIs and as augmentation in 1 patient unable to tolerate high doses of an SRI. Inositol was reasonably well tolerated, and time to response in these patients varied between 4 and 8 weeks. Given that hair pulling can recur after initial improvement,<sup>13</sup> longer follow-up is needed to determine if initial treatment response is sustained for Ms. A and Ms. B. Two of the 3 patients had comorbid major depression, which also resolved on inositol treatment. Interestingly, 1 patient who complained of a decrease in libido on citalopram (Ms. A) reported improvement when inositol was added. Inositol's effects, if any, on sexual functioning have not been reported in the literature. Since 8 to 16 weeks is sometimes needed for skin picking to decrease, early improvement of Ms. A's skin picking might, in part, have been due to "carryover" effects of initial citalopram treatment.

Inositol has been shown to be effective in OCD and other psychiatric disorders (depression, panic disorder) responsive to SRIs, but not in disorders (e.g., schizophrenia, Alzheimer's disease) not responsive to SRIs.<sup>14</sup> In a placebo-controlled, crossover trial of inositol in OCD,<sup>9</sup> 10 of 13 patients entered responded favorably to inositol. All 10 responders were noted to have responded well or partially to SRIs in the past. The 3 non-responders had been resistant to prior SRI treatment. A recently published double-blind, randomized, crossover trial of inositol (18 g/day) versus placebo augmentation of SRIs in 10 OCD patients<sup>15</sup> showed no significant difference between the 2 treatment phases.

Open-label case reports such as these have obvious limitations. Nevertheless, the 3 cases described here suggest that inositol might be a treatment option in some patients with hair pulling and skin picking and could be considered in patients who tolerate SRIs poorly or who are unwilling to take them. Further research on inositol in other putative obsessive-compulsive spectrum disorders would be of interest.

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#### Hypothermia in 2 Patients Treated With Atypical Antipsychotic Medication

**Sir:** Atypical antipsychotics such as olanzapine, risperidone, and quetiapine are commonly prescribed by psychiatrists because of their efficacy and minimal extrapyramidal side effects. Some of the common side effects include somnolence, anticholinergic effects, and orthostatic hypotension. In the 2 cases that follow, we found a common thread between patients' taking atypical antipsychotics and hypothermia, a side effect not mentioned in the drug profile. Our recent literature search found 1 other published case report<sup>1</sup> of atypical antipsychotic treatment associated with hypothermia.

**Case 1.** Ms. A, an 83-year-old white psychiatry inpatient with a medical history of bipolar disorder, dementia, catatonia, hypertension, and chronic urinary tract infections on suppression therapy, presented to the emergency department with a 2-week history of declining mental status. Her caregiver reported that Ms. A had a decrease in oral intake during the last 2 weeks and that her last documented bowel movement was 3 days prior. For the previous few days, there had been a notable decline in her mental status and level of activity. Ms. A became more withdrawn and nonverbal from baseline. On arrival at the emergency department, she was obtunded, with a core rectal temperature of 91.6°F (33.1°C). She had no history of cold exposure.

Allergies and/or adverse effects associated with penicillin, amitriptyline, and perphenazine were noted, but the type of reaction was not documented. There was also mention of sensitivity to neuroleptics. Current medications at admission were lithium carbonate, 300 mg b.i.d., with an additional 600 mg at bedtime; piroxicam, 20 mg q.d.; clonazepam, 1 mg q.h.s.; trazodone hydrochloride, 25 mg b.i.d.; lactulose, 10 mg q.h.s.; sulfamethoxazole, 800 mg-trimethoprim, 160 mg q.d.; and olanzapine, 5 mg q.d. Olanzapine had been started 3 weeks prior to admission.

Ms. A's physical examination was significant for a rectal temperature of 91.6°F (33.1°C), blood pressure of 122/40 mm Hg, pulse rate of 85 b.p.m., and an oxygen saturation of 96% with room air. She was nonverbal. Her mucous membranes were moist, and there was no exophthalmos, goiter, or neck masses. Her lungs were clear bilaterally, and her heart sounds were normal. Her breast examination was negative for masses, and her abdomen was soft and nontender. Examination of Ms. A's extremities demonstrated mild 1+ pitting edema of the right ankle. Neurologic examination demonstrated lethargy and flinching to substernal rub with her eyes closed. Her plantar reflex was downgoing bilaterally, and her deep tendon reflex was 2+ with no delay in relaxation.

Laboratory data included the following values: negative results from a urinalysis, serum lithium level of 2.2 mEq/L (therapeutic range, 0.6–1.2 mEq/L), and a complete blood count showing a white blood cell (WBC) count of  $4.5 \times 10^3/\text{cm}^3$ , a hemoglobin concentration of 15.6 g/dL, a hematocrit of 39.9%, a platelet count of  $104 \times 10^3/\text{cm}^3$ , and a mean corpuscle volume of 85 mm<sup>3</sup>. Profile II revealed the following serum levels: sodium, 142 mEq/L; potassium, 4.4 mEq/L; chloride, 109 mEq/L; carbon dioxide, 23 mEq/L; serum urea nitrogen, 30 mg/dL; creatinine, 1.0 mg/dL; glucose, 86 mg/dL; and calcium, 9.8 mg/dL. Liver enzymes were within normal limits except for a mildly elevated aspartate aminotransferase (AST) level of 51 U/L. Electrocardiogram demonstrated normal sinus rhythm without an Osbourne wave. Imaging studies included computed tomography of the head and chest x-ray, which showed no abnormalities.

Ms. A was admitted for observation and was given warm intravenous hydration and heated blankets. All medications were held. Blood cultures and urine cultures were negative. Results of thyroid function studies were within normal ranges, including thyrotropin, free thyroxine (T<sub>4</sub>), and triiodothyronine (T<sub>3</sub>). Random and early morning cortisol levels were checked and also were within normal limits. On day 2, Ms. A's rectal temperature had increased to 96.0°F (35.6°C), and by hospital day 3 it was 97.6°F (36.5°C). Her mental status had also improved. Lithium was restarted, and she was transferred back to the psychiatric facility.

**Case 2.** Ms. B, a 68-year-old white psychiatry inpatient, had a medical history of hypertension, congestive heart failure, congenital immunoglobulin class G (IgG) deficiency currently controlled with intravenous IgG, type 1 diabetes mellitus, schizophrenia, and hypothyroidism status after thyroidectomy. She presented to the emergency department with a systolic blood pressure of 80 mm Hg and tympanic temperature of 92.0°F (33.4°C). She had recently been admitted with similar symptoms of lethargy and hypothermia. She had no recent cold exposure.

Current medications included valproic acid, 750 mg every 6 hours; estradiol, 1 mg q.h.s.; clonazepam, 1 mg t.i.d.; fluphenazine, 5 mg b.i.d.; hydroxyzine, 50 mg t.i.d.; lisinopril, 2.5 mg q.d.; levothyroxine, 62.5 µg q.d.; folic acid, 1 mg q.d.; insulin NPH, 14 units q.d.; nitroglycerin patch, 0.2 mg q.d.; furosemide, 40 mg q.d.; and quetiapine, 100 mg b.i.d. Quetiapine was started 1 week prior to admission.

On physical examination, Ms. B was delusional and combative. She had a core rectal temperature of 90.0°F (32.0°C), and her systolic blood pressure ranged between 80 and 110 mm Hg, with a pulse rate of 65 b.p.m. Results of head and neck examinations were unremarkable except for a surgical scar. Her mucous membranes were moist without pallor. Heart sounds were distant. Her chest was clear to auscultation with a clean port-a-cath site. Her abdomen was obese, soft, and nontender with bowel sounds. Her skin was dry and cool. Neurologically, Ms. B had intact reflexes and no gross motor deficit.

Laboratory data included the following values: negative results from a urinalysis and a complete blood count revealing a WBC count of  $4.8 \times 10^3/\text{cm}^3$ , a hemoglobin concentration of 8.9 g/dL, a hematocrit of 26.3%, and a platelet count of  $145 \times 10^3/\text{cm}^3$ . Profile I showed the following serum levels: sodium, 142 mEq/L; potassium, 4.5 mEq/L; chloride, 106 mEq/L; carbon dioxide, 26 mmol/L; glucose, 102 mg/dL; serum urea nitrogen, 15 mg/dL; and creatinine, 0.7 mg/dL. Two sets of blood cultures yielded no growth after 3 days.

Ms. B was admitted for 3 days, during which time she received warmed intravenous fluids and heated blankets. Results of random cortisol and thyroid function studies were within normal limits. Medications were stopped. She was initially treated with antibiotics, which were subsequently discontinued when the cultures were negative.

Of note, Ms. B had been admitted twice previously for hypothermia, which was attributed to a urinary tract infection, since no other cause was found. On both occasions, she had been taking an atypical antipsychotic drug (olanzapine or quetiapine). However, on the third admission, there was no evidence of infection, and the possibility of a drug side effect was entertained. She was discharged back to the psychiatric facility after discontinuation of her atypical antipsychotic medication. One month later, she was restarted on olanzapine, 10 mg q.d., and, to our knowledge, has not had a recurrence of hypothermia.

In both cases, the most common causes of hypothermia, such as hypothyroidism, infection, and cold exposure, were ruled out owing to results of laboratory work and the lack of recent exposure to a cold environment. These cases were observed in September, and both patients were inpatients in psychiatric facilities. Potential hypothermia-inducing medications that the patients were taking, such as clonazepam and lithium, were considered as possible causes. Clonazepam was eliminated secondary to the length of time the patients had been taking the drug without inducing hypothermia. One patient had mildly elevated lithium levels, but her thyroid hormone levels were within normal limits. In both cases, a new atypical antipsychotic was introduced 1 to 3 weeks before the subsequent hypothermic episode; thus, we considered the potential of a drug-induced hypothermic event.

Our review of the literature identified a single case report of a 37-year-old woman with psychosis in association with Prader-Willi syndrome who experienced hypothermia initially while being treated with risperidone and again when switched to olanzapine.<sup>1</sup> Upon cessation of antipsychotic drug treatment, the hypothermia resolved. Hypothyroidism was excluded as a cause on the basis of normal results of thyroid function tests.

Although the exact mechanistic action of the atypical antipsychotics is unknown, it has been proposed that the antipsychotic activity is mediated through a combination of dopamine (D<sub>1-4</sub>) and 5-hydroxytryptamine-2 (5-HT<sub>2</sub>) antagonism. Antagonism at α<sub>1</sub>, muscarinic (M<sub>1-5</sub>), and histamine receptors are thought to be responsible for orthostatic hypotension, anticholinergic effects, and somnolence, respectively.<sup>2,3</sup>

Neuroleptics as a class of drugs have been known to be poikilothermic agents. In fact, the older neuroleptics such as chlorpromazine and haloperidol can cause hypothermia and have been used to induce hypothermia in experimental models.<sup>4-7</sup> Both of these drugs also have hyperthermia and hypothermia listed as possible overdose symptoms in standard drug manuals.<sup>8</sup> Although no clinical studies demonstrating atypical antipsychotic-induced hypothermia are known to the authors, one study<sup>9</sup> found that clozapine, olanzapine, and risperidone induced hypothermia in rats. The hypothermia produced by clozapine was fully antagonized by a dopamine D<sub>1</sub> receptor antagonist, whereas the hy-



pothemia produced by olanzapine and risperidone was not. The data thereby indicated a dopamine D<sub>1</sub> mechanism for clozapine-induced hypothermia and precluded this mechanism for olanzapine and risperidone. Olanzapine, risperidone, and quetiapine were found to have an antagonistic effect at dopamine D<sub>2</sub> receptors, with no evidence for dopamine D<sub>1</sub> receptor-mediated hypothermia, whereas clozapine was determined to be a partial agonist at dopamine D<sub>1</sub> receptors. It is likely that olanzapine and risperidone mediated their hypothermic effect through antagonism at receptors other than dopamine.

In the hypothalamus, 5-HT has been reported to be important in temperature regulation.<sup>10</sup> Several studies have indicated that 5-HT<sub>2</sub> agonists increase body temperature in rodents and humans.<sup>10-12</sup> 5-HT<sub>2</sub> agonists have been shown to inhibit the hypothermic effect of chlorpromazine and haloperidol in mice.<sup>4</sup> In addition, elevation in 5-HT levels in the hypothalamus may result in hyperthermic effects, whereas lowering 5-HT levels may result in lowering body temperature.<sup>13</sup> Indeed, studies employing chlorpromazine and apomorphine for induction of hypothermia have shown enhanced hypothermia with serotonin suppression and in conjunction with serotonin antagonists.<sup>14,15</sup> By antagonizing hypothalamic 5-HT<sub>2</sub> receptors, atypical antipsychotics most likely reduce the body's ability to adequately regulate internal temperature. Likewise, antagonism of postsynaptic 5-HT<sub>2</sub> receptors may reduce the interaction between 5-HT and the receptor and cause an effective reduction in 5-HT.

In the peripheral nervous system, it is well known that  $\alpha_1$  receptors are responsible for vasoconstriction and shunting of blood away from the skin to maintain core body temperature. Owing to the atypical antipsychotic  $\alpha_1$  antagonism, inhibition of blood shunting may potentiate heat loss through the skin. Alpha-1 antagonists such as prazosin and terazosin have been shown to induce and potentiate hypothermia.<sup>16-18</sup> Thus, the antagonism of both 5-HT<sub>2</sub> receptors within the hypothalamus and  $\alpha_1$  receptors peripherally may have an effect on the ability to adequately maintain core body temperature and reduce the hypothalamic thermoregulatory response.

We propose that possible mechanisms for olanzapine-, quetiapine-, and risperidone-induced hypothermia may include (1) an initial decrease in peripheral vasoconstriction through  $\alpha_1$  antagonism, (2) a blunted hypothalamic thermoregulatory response to heat loss due to antagonism at the 5-HT receptors in the hypothalamus, and (3) hypothermia as a result of lessened 5-HT interaction with 5-HT<sub>2</sub> receptors in the hypothalamus. More research is needed in this area to prove such a cause and effect; however, clinicians should be aware of this potentially dangerous side effect.

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