Letters to the Editor

Upper-Extremity Self-Amputation in a Case of Dissociative Identity Disorder

Sir: Dr. Schlozman's recent article[1] reviewing 13 documented cases of self-amputation is an important contribution, which hopefully will encourage more clinicians, like myself, to add to the reports in the literature. He notes that all the patients were psychotic (schizophrenic or psychotic depression), with a preponderance of guilt and religious preoccupation related to sin and punishment. Eleven of the patients were men and few were acutely suicidal; indeed, the self-amputation may have helped to contain and localize the self-destructive impulse to the hand, which is then severed to get rid of the defective or offending body part. I am essentially in agreement with his conclusions, but wish to add another diagnostic category to the series—the profoundly traumatized individual with a dissociative disorder, especially dissociative identity disorder, formerly known as multiple personality disorder. Such patients may be chronically suicidal with periods of greater impulsivity and higher risk.[2–4]

Case report. Ms. A, a 37-year-old married mother of 2, was readmitted to the psychiatric unit for an upsurge of suicidal feelings and urges to amputate her left hand by placing it under an approaching train. She could not see how this plan would have jeopardized her whole body, i.e., her life, insisting that she would feel much better to have the hand removed. The patient had been sexually abused in childhood by an uncle and brutally gang raped in college. She never forgave herself for not being able to defend herself and wished they had killed her instead. Her left hand did "bad things" and came to symbolize all of her sexual "sins," a finding described by Dr. Schlozman in many of the other cases. She had cut her left wrist several times in the past, sustaining nerve damage that left it numb but not paralyzed; a paralyzed hand was a second choice to frank amputation.

At the time of admission, she also had a self-induced osteomyelitis of a finger that she hoped would spread and require amputation by the surgeons, another option in case she could not get to the train. All of these self-inflicted injuries occurred while Ms. A was in an autohypnotic, amnestic, fugue-like state that she experienced as a malevolent "alter personality" named "the unknown one." When she learned that the osteomyelitis was responding to antibiotics and her finger would be spared, she went into a silent rage. One evening, while Ms. A was still hospitalized, "the unknown one" reemerged and severed the finger with the sharp edge of a soda can, flushing the digit down the toilet so it could not be reattached. When Ms. A "returned," she was blasé and somewhat relieved by the amputation, much to the horror and shock of the staff. The "curative" effects of this self-amputation lasted several months when an upsurge of impulses to "complete the job" necessitated readmission to the hospital.

In her defensive altered state, Ms. A was convinced that her left hand should be amputated, which was a disguised, dissociated suicidal wish. She was haunted by flashbacks, traumatic dreams, and gustatory hallucinations related to her trauma, which were not amenable to any pharmacologic intervention. In addition, a comorbid recurrent affective disorder was also considered, but a severe eating disorder resulting in dehydration, electrolyte imbalance, and hypotension limited medication strategies. She was treated with long-term intensive outpatient psychotherapy, residential living, and intermittent acute hospitalization when the urges to complete the amputation of the hand became overwhelming.

Despite these efforts, the "unknown one" secretly planned the amputation of another finger on the left hand about a year later. It was deftly performed with a hacksaw, and the digit was discarded before the patient calmly drove herself to the emergency room. Interestingly, following this bizarre act, she made important gains in therapy. Nevertheless, her prognosis remains rather guarded, and she continues in active treatment.

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Dr. Schlozman Replies

Sir: I am grateful for the opportunity to respond to Dr. Brenner's case report detailing the possible link between dissociative identity disorder and upper-extremity self-amputation. It is fascinating to note that many of the symptoms that appear to accompany these severe acts of self-mutilation—the belief that one's hand has behaved badly and therefore needs to be removed, the seeming calm and increased organization that follow such an act, and the apparent lack of appreciation for the seriousness of the act—all are consistent with classically described dissociative symptoms. Although I have not heard of any cases (until now) of more definitive dissociative symptoms surrounding acts of self-amputation, it is entirely possible that a dissociative state would more easily facilitate such drastic actions as a means of resolving internal conflicts.

Since the article to which Dr. Brenner is responding was published, numerous colleagues have approached me to describe similar cases that were not formally documented as case reports. It seems that upper-extremity self-amputation is more common than the literature suggests. Hopefully, as more cases are de-

scribed, the heterogeneity and treatment options for this trying situation can be increasingly delineated. I welcome Dr. Brenner's case report as a valuable contribution toward this effort.

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Anetholtrithion Stabilizes Body Weight Fluctuation Caused by Excessive Water Drinking in a Patient With Schizophrenia: A Case Report

Sir: Treatment approaches for schizophrenic patients manifesting severe polydipsia include changing antipsychotic drugs, changing drug dosage, and stopping anticholinergic drugs used to treat movement disorders. Antipsychotic drugs and smoking are thought to contribute to polydipsia in schizophrenia, but the exact cause remains unknown.[1] Some schizophrenic patients are placed in isolation to restrict access to water and, thus, prevent dilutional hyponatremia and subsequent generalized seizures. We need better treatments for severe polydipsia in schizophrenia.

Anetholtrithion is used in dental treatment of patients suffering from dysfunction of the salivary gland.[2] It effectively relieves dry mouth, which has been purported to be an etiologic factor in polydipsia. Anetholtrithion is known as a cholinergic stimulant; however, this agent is not to be considered as a simple cholinergic agonist.[3] We report a case in which treatment with anetholtrithion was effective in moderating excessive water drinking. The effectiveness of the treatment was based on the percent maximum weight gain (PMWG = [maximum diurnal weight – standard weight] × 100/standard weight).[4] Standard weight was defined as the mean of daily morning body weights measured during the 4 months prior to treatment. Body weight was measured 4 times a day during anetholtrithion administration.

Case report. Mr. A, a 41-year-old man who met DSM-IV criteria for schizophrenia, undifferentiated type, had been receiving psychiatric treatment for more than 15 years. He reported feeling thirsty and drank water excessively. He had been locked in his room to prevent excessive drinking on 3 occasions during his hospital admission. Changes in the major tranquilizer prescribed to him and its dosage did not attenuate excessive drinking. Mr. A's standard body weight was 57.4 kg. The maximum PMWG during the 4 months prior to treatment was 9.05% (range, –5.25% to +9.05%). Without changing any other medication, anetholtrithion, 25 mg, was administered orally 2 hours before every meal (75 mg/day). After 2 weeks, Mr. A reported that he felt less thirsty. His mean body weight decreased weekly, and after 4 weeks of treatment, it was 1.73 kg less than his standard weight. The maximum PMWG over the 4 weeks of treatment was 1.81% (range, –7.69% to +1.81%). We observed no side effects, and Mr. A reported no side effects.

Anetholtrithion is not widely used in psychiatric treatment, and Bagheri et al.[5] have reported that the increase in salivary flow is greater with yohimbine than with anetholtrithion. However, anetholtrithion is used commonly in dental treatment, so the risk and incidence of side effects are well documented. Our experience with this patient suggests that anetholtrithion may be effective treatment for pathologic polydipsia among certain patient populations. Anetholtrithion is most likely to be effective when (1) the patient experiences excessive thirst or dry mouth and (2) drinking behavior is not involved in his or her delusions. Anetholtrithion may also be effective in patients whose dry mouth and thirst are side effects of major tranquilizer use.

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Relative Weight Gain Among Antipsychotics

Sir: In his October 1998 BRAINSTORMS on weight gain associated with psychotropic drugs, Dr. Stahl grouped risperidone together with clozapine and olanzapine as causing minimal short-term weight gain and moderate long-term weight gain.[1] This is misleading.

Although risperidone can cause an increase in weight, it does not produce nearly the amount of weight gain seen in patients receiving olanzapine or clozapine.[2] In the analysis by Allison et al.[3] of 78 studies of patients receiving atypical antipsychotics, mean weight gain increases after 10 weeks of treatment were as follows: clozapine = 4.45 kg (9.8 lb), olanzapine = 4.15 kg (9.1 lb), risperidone = 2.10 kg (4.6 lb), and ziprasidone = 0.04 kg (0.1 lb). In their comparative 8-week study of risperidone and clozapine (N = 86), Bondolfi et al.[4] reported a weight gain of 2.7 kg (5.9 lb) in the clozapine group ($p < .01$) and a nonsignificant weight gain of 1.1 kg (2.4 lb) in the risperidone group. In their comparative 8-week study of risperidone and olanzapine (N = 407), Conley et al.[5] reported that patients receiving risperidone gained significantly less weight than patients receiving olanzapine (mean ± SD = 4.6 ± 0.9 vs. 8.6 ± 0.9 lb [2.1 ± 0.4 vs. 3.9 ± 0.4 kg], $p < .001$), and the change in body mass index was significantly less in the risperidone-treated patients (0.7 ± 0.1 vs. 1.3 ± 0.1, $p < .001$). In long-term studies, patients receiving risperidone had a mean weight gain of 3.3 kg (7.3 lb) after 1 year of treatment, whereas patients receiving olanzapine had a mean weight gain of 8 to 12 kg (17.6 to 26.4 lb).[6,7]

The differences in weight gain among the atypical antipsychotics have been attributed to the degree of affinity of the drug for the serotonin-2C ($5\text{-}HT_{2C}$) and histamine-1 (H_1) receptors.[8] Olanzapine has a higher affinity for H_1 receptors than does risperidone,[9] and the ratio of $5\text{-}HT_{2A}/5\text{-}HT_{2C}$ receptors bound by risperidone is 100-fold greater than the ratio of these receptors bound by olanzapine or clozapine.[10]

The atypical antipsychotic drugs do have a more favorable side effect profile than conventional neuroleptics; for example, the incidence of extrapyramidal symptoms is much lower than with conventional neuroleptics. However, the weight gain associated with some atypical antipsychotics can pose serious health

risks. Obesity is strongly linked with numerous health problems including hypertension, diabetes, heart disease, and some forms of cancer. Clozapine and olanzapine have been shown to promote the onset of diabetes or exacerbate preexisting diabetes.[11,12] Even small amounts of weight gain can lead to serious health issues over time. For example, a weight gain of only 11 lb (5 kg) can significantly increase the risk of heart disease.[13] The weight gain from neuroleptics not only can contribute to the onset of secondary problems for patients but also can lead to noncompliance, another factor that can put patients at health risk.[14]

I strongly agree with Dr. Stahl that clinicians should regularly monitor patients' body weight during antipsychotic drug therapy, in addition to implementing a program of routine exercise and proper nutrition. Selection of the appropriate antipsychotic for patients should be done in consideration of the patients' psychological as well as physical status. Although the atypical antipsychotics are currently the treatment of choice for patients with schizophrenia and other related disorders, the weight gain associated with some of these drugs should be considered. Psychiatrists need to address patients' concerns about adverse effects and manage weight gain to prevent or reduce the risk of medical illness and relapse.

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Dr. Stahl Replies

Sir: I am very pleased that Dr. Masand has become one of the champions in psychiatry for promoting better recognition and treatment of the weight gain and obesity that psychotropic drugs can cause.[1,2] I also agree with him that some atypical antipsychotics cause more average weight gain than others in clinical trials and have in fact written about this in a recent scholarly review[3] and in my recent textbook.[4] Table 1 is adapted from these publications and is a rank-order meta-analysis of those few studies that have reported on this important problem in psychiatry.[3–7] In addition to demonstrating Dr. Masand's main point, namely greater weight gain with olanzapine than with risperidone,[1] Table 1 also puts the weight gain of several other antipsychotics in context. Hopefully, this amplification will eliminate anything that may have been confusing or misleading in the table entitled "Possible effects of selected psychotropic drugs on weight gain" that was recently published in a Brainstorms feature.[8]

Even Table 1 could be misleading to the prescriber of antipsychotics. To such prescribers, what is most important is not the *average* weight gain for a *population* of patients treated with one antipsychotic versus another, but *clinically important weight gain* for the *individual* patient treated with any antipsychotic drug. Thus, atypical antipsychotics—some more than others—not only frequently cause minimal-to-moderate weight gain in the average patient, but occasionally are associated with large increases in body mass index into the overweight range (> 24–25) or especially into the obese range (> 30), where medical risks develop[9] as emphasized by Masand.[1] These are the patients who need our attention as prescribers with aggressive monitoring, both to prevent obesity by recognizing weight gain early in treatment and to treat obesity if it develops or worsens.

Potential mechanisms of action for differences in weight gain observed with different antipsychotic drugs were discussed by Masand[1] and in a previous Brainstorms.[10] Although differences in affinity for both 5-HT_{2C} receptors and H_1 receptors have been proposed as explanations for differences in liability for weight gain of various antipsychotics,[7,10] affinity for the H_1 receptor seems to be more important because there is a better correlation of weight gain with affinity for this receptor than with affinity for the 5-HT_{2C} receptor.[7] Furthermore, ziprasidone, which has the lowest weight gain among the atypical antipsychotics, is actually a high-affinity antagonist of the 5-HT_{2C} receptor.[11]

Table 1. Weight Gain and Antipsychotics[a]

No change or weight loss
Loxapine
Molindone
Increasing likelihood of weight gain
Ziprasidone (the least weight gain)
Thiothixene
Fluphenazine
Haloperidol
Risperidone
Chlorpromazine
Sertindole
Quetiapine
Thioridazine
Olanzapine
Zotepine
Clozapine (the most weight gain)

[a]Data from references 3–7.

Hopefully, the debate about psychotropics and weight gain will be framed as "What do we do about the fact that psychotropic drugs can cause obesity and that this is frequently not recognized or treated by prescribers of these drugs?" A discussion about which psychotropic drug causes the worst weight gain risks missing this point and is a bit like the story of the 2 speeders caught by a traffic cop, one of them arguing he should be let go without a ticket because he was speeding more slowly than the other guy. Speeding is speeding. Clinically significant weight gain is clinically significant weight gain. Appropriate attention to this issue should improve the quality of life for patients treated with psychotropic drugs.

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Venlafaxine Versus Fluoxetine

Sir: The randomized controlled trial of venlafaxine and fluoxetine reported by Costa e Silva concludes that the results support "the efficacy and tolerability of venlafaxine in comparison with fluoxetine for treating outpatients with major depression."[1(p352)]

With regard to tolerability, there would appear from the raw data reported to be differences that favor fluoxetine with respect to nausea, headache, dizziness, somnolence, trembling, diaphoresis, anxiety, and dry mouth. Overall, 181 treatment-emergent adverse effects were reported with venlafaxine and 91 with fluoxetine. Differences of the magnitude quoted are likely to be clinically relevant and, given that 382 patients were included in the trial, statistically significant as well. It is curious that side effects are reported at the end of week 1 in an 8-week trial. There are few data to support the use of fluoxetine in doses greater than 20 mg for the treatment of depression.[2] Side effects are dose related. The trial design, which allowed the dosage of fluoxetine to be increased to 40 mg/day, therefore, favored venlafaxine, but still found fluoxetine to be significantly better tolerated. In addition, it is reported that statistically significant increases in blood pressure were found in the venlafaxine-treated patients. While the mean increases were reported, neither the standard deviations nor the ranges were, making it difficult to determine the clinical significance of these changes.

With regard to efficacy, the study found no difference between the 2 treatments at endpoint, but reported increased efficacy of venlafaxine over fluoxetine in the subgroup of patients treated with a higher dose. Does this mean that venlafaxine was less effective than fluoxetine at standard doses?

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Lamotrigine as Prophylaxis Against Steroid-Induced Mania

Sir: Corticosteroid therapy, used to treat a variety of inflammatory diseases, can cause severe mood changes and psychosis in a subgroup of patients.[1] This case suggests that lamotrigine, a new anticonvulsive drug with mood-stabilizing effects,[2] may prevent steroid-induced mania in patients for whom lithium or valproate treatment is not possible.[3,4]

Case report. Ms. A, a 41-year-old woman with a 28-year history of bipolar disorder previously controlled on lithium, 900 mg/day, presented for admission with reduced sleep, psychomotor agitation, pressured speech, racing thoughts, and labile affect. Ms. A's Mini-Mental State Examination score was 28/30, and her Brief Psychiatric Rating Scale (BPRS) score (of 38) was positive for manic symptoms of disorganization, excitement, grandiosity, suspiciousness, uncooperativeness, anxiety, and tension.

Ms. A had a 2-year history of nephrogenic diabetes insipidus and hypertension. Two months prior to admission, following further deterioration in her renal function (serum creatinine level = 2.4 mg/dL, serum urea nitrogen level = 42 mg/dL), a biopsy led to the diagnosis of interstitial nephritis, most likely secondary to long-standing lithium use. Ms. A's medications prior to admission included perphenazine, 32 mg/day; temazepam, 30 mg at bedtime; lorazepam, 1 mg every 8 hours; nifedipine, 10 mg every 12 hours; as well as lithium, 900 mg/day, with a plasma level of 0.68 mEq/L. Although an increase in the lithium dose was indicated to control manic symptoms, especially in the context of a pending steroid trial,[1] lithium was not an option because of her renal dysfunction and was discontinued over the first 5 days after admission.

A valproate trial was rejected because of a prior history of intolerable side effects. Lamotrigine was started on admission at 25 mg every 12 hours and, over a 9-day period, increased to 200 mg every 12 hours. On the second day after admission, lorazepam was replaced with clonazepam (1–1.5 mg b.i.d.) to control breakthrough anxiety. For treatment of interstitial nephritis, pred-

nisone was started on the third day at 40 mg/day and increased by the ninth day to a total daily dose of 120 mg. As the lamotrigine dose was increased, Ms. A's manic symptoms decreased despite concomitant steroid therapy at significant doses. A prednisone taper was started on the tenth day, and she was discharged on the eleventh day on 40 mg/day of prednisone. Her BPRS score at the time of discharge was 18 (a 47% decrease) and 6 weeks later was 15, reflecting further improvement.

Lamotrigine is a new anticonvulsant, reported to have mood-stabilizing effects through inhibition of excessive release of excitatory amino acids such as glutamate.[2] Prior work has suggested that lamotrigine can be effective in the treatment of refractory bipolar disorder.[5] To our knowledge, this is the first report suggesting that lamotrigine may also prevent steroid-induced mania in patients at risk. In this case, it could be suggested that perphenazine, nifedipine, or clonazepam treated the patient's manic symptoms.[6,7] However, perphenazine and nifedipine were administered for at least 2 months prior to admission and clonazepam was an equivalent replacement for an existing benzodiazepine regimen, whereas response in this patient correlated with increased lamotrigine dose. These findings support reports of remission of manic symptoms with lamotrigine[2,5] and suggest that lamotrigine can be effective in the prevention of steroid-induced mania.

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Reserpine Treatment of Comorbid Tourette's Disorder and Tardive Dystonia

Sir: Despite increases in the understanding of the course, psychopathology, and pathophysiology of Tourette's disorder, the use of neuroleptic medication is still a mainstay of the treatment,[1] leaving the afflicted person vulnerable to the development of tardive dyskinesia or dystonia. Moreover, the treatment of severe forms of tardive dyskinesia or dystonia has been difficult, especially in young people.[2–4]

We report the successful treatment of a young person who developed tardive dystonia in the course of treatment of Tourette's disorder with haloperidol.

Case report. Mr. A, a 20-year-old Hispanic man, was diagnosed at age 14 with moderate mental retardation and DSM-IV Tourette's disorder. His Tourette's disorder symptoms were limited to facial tics (periorbital and nasal) and coprolalia. He had been maintained on haloperidol, 2 to 4 mg p.o. q.d., for 6 years with good symptomatic relief. A routine ophthalmologic examination 6 months prior to this hospital admission revealed increased intraocular pressure in his right eye, and haloperidol was discontinued. Mr. A was started on risperidone, 1 mg p.o. b.i.d., as well as timolol 0.5%, 1 drop in each eye q.d.

After the discontinuation of haloperidol, Mr. A became more anxious, and his outpatient psychiatrist started him on treatment with buspirone, in addition to the risperidone, with poor results. His anxiety intensified, and he developed progressively increasing lethargy, episodic tachycardia, and diaphoresis along with panic-like anxiety, loss of appetite, depressed mood, and reduced ability to function in his group home. Facial tics and coprolalia returned.

Mr. A was then referred to our institution. Examination revealed a prominent movement disorder that included facial grimacing, wrinkling of the nose, eye blinking, athetoid movements of the hands and arms, and hyperextensive dystonic movements of the torso and neck. His gait showed a lordotic posture with a tendency to jerk his arms and elevate them, shoulder shrugging, toe walking, difficulty standing up, and the necessity to run from one place to another to avoid interfering dystonic movements. The athetoid movements left him unable to eat without assistance. There were periods of forceful breathing and shortness of breath accompanied by an increase in pulse and blood pressure. These periods were often followed by abdominal pain, polyuria, and polydipsia.

Mr. A's condition deteriorated progressively in the 6 months after haloperidol discontinuation. An endocrinological workup ruled out Wilson's disease, carcinoid syndrome, pheochromocytoma, insulinoma, and diabetes mellitus. At admission, risperidone and buspirone were discontinued and nefazodone started because of prominent depressive symptoms. When the neuroendocrinologic workup was complete, we elected to treat him with reserpine, 0.25 mg p.o. q.i.d., with a gradual increase to 1 mg p.o. q.i.d. Nefazodone was discontinued. There was a gradual and marked improvement in the movement disorder. However, Mr. A continued to experience an irregular respiratory rate and rhythm, transient shortness of breath, and significant abdominal pain with elevation of pulse and blood pressure. We believed this represented continued respiratory dyskinesia.[5] Treatment with diazepam, 5 mg p.o. t.i.d., which was later changed to clonazepam, 1.5 mg p.o. q.d., improved these symptoms. At the time of discharge, Mr. A was able to walk and eat without assistance, and anxiety was minimal. There were no jerking movements, although there were occasional irregularities of respiratory rate. There was no evidence of either facial tics or coprolalia.

In a follow-up call to the family 8 months after discharge, it was reported that there was no evidence of dystonic movements and no evidence of either tics or coprolalia. Mr. A was still maintained on reserpine, 1 mg p.o. q.i.d., and clonazepam, 1.5 mg p.o. q.d.

Tardive dystonia can be defined as a neuroleptic-induced, late-onset, persistent movement disorder consisting of sustained involuntary twisting movements affecting the limbs, trunk, neck, or face.[6] It has been shown that younger patients suffer more prominent movements.[3,4] At the same time, respiratory dyskinesia is a common but underrecognized side effect of chronic neuroleptic administration.[5] The effect of age on the topographic distribution of tardive dyskinesia and dystonia bears some re-

semblance to phenothiazine-induced acute dystonic reactions and idiopathic torsion dystonia, in which children and adolescents tend to suffer generalized axial movements whereas adults often manifest more localized face and neck involvement.[7]

A wide range of pharmacologic treatments have been used in an attempt to decrease these symptoms: dopaminergic-receptor antagonists, dopaminergic-depleting drugs, dopaminergic drugs, cholinergic agonists, and GABA-agonist drugs.

We chose reserpine because of its catecholamine-depleting properties and with the assumption that the dystonia was due to a dopamine receptor supersensitivity. Reserpine has been used to treat coexisting psychosis and tardive dyskinesia,[8] and we speculated that it would help relieve the symptoms of coexisting Tourette's disorder and tardive dystonia. Previous reports indicated that benztropine and tetrabenazine were not helpful and clonazepam only partially helpful for tardive dystonia.[6]

Reserpine proved to be quite effective in this instance, and we would agree with Healy and Savage that its use needs to be "exhumed."[9]

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Adding Other Antipsychotics to Clozapine

Sir: When faced with treatment-refractory schizophrenic patients, an increasing number of clinicians are adding other antipsychotics to clozapine[1] with the idea of increasing the blockade of D_2 receptors. We are not aware of prior description of the combined use of clozapine and perphenazine.

Case report. Mr. A, a 46-year-old white male smoker (10 cigarettes per day, an amount that has been stable during this study period), was hospitalized with a diagnosis of schizoaffective disorder and had been taking 400 to 500 mg/day of clozapine and 15 mg/day of haloperidol for 6 months (plasma levels ranged from 557–823 ng/mL for clozapine, 185–303 ng/mL for norclozapine, and 5.7–11.6 mg/L for haloperidol). Other medications included valproate, benztropine, and clonazepam. Mr. A vaguely reported he had "felt better" in the past on perphenazine therapy. Therefore, at his request, he was taken off haloperidol and switched to perphenazine (with a gradually increasing dose of 24 to 48 mg/day) without changes in clozapine dose (450 mg/day).

Within 3 weeks, Mr. A's psychosis worsened, and he complained of myoclonus and hypersalivation. Plasma clozapine levels were more than doubled the ninth day after the perphenazine dose was increased to 48 mg/day (clozapine level = 1451 ng/mL; norclozapine level = 484 ng/mL) and 2 days later even though Mr. A had refused a 350-mg dose of clozapine on the previous night (clozapine level = 1162 ng/mL; norclozapine level = 469 ng/mL; perphenazine level = 19 ng/mL; valproate levels remained stable). Perphenazine was stopped, and the prior dose of haloperidol was restarted. Eight days later, clozapine levels returned to their prior range (clozapine level = 693 ng/mL; norclozapine level = 222 ng/mL). Myoclonus, hypersalivation, and the worsening of psychosis (including a reappearance of serious threatening behavior) decreased with resumption of haloperidol.

The literature suggests that plasma clozapine levels greater than 350 ng/mL may be associated with therapeutic response and that seizures may be associated with plasma levels higher than 1000 ng/mL,[2] but plasma antipsychotic levels are often not obtained in clinical practice. Perphenazine metabolism is primarily mediated by cytochrome P450 (CYP) 2D6.[3] Clozapine metabolism is attributed mainly to CYP1A2 and CYP3A4[4]; CYP2D6 is not thought to play a major role. Without having done therapeutic drug monitoring, the treating physician might have concluded 3 other possible explanations for the worsening of psychosis: the adverse effects of perphenazine alone, an exacerbation of Mr. A's underlying disease, or the inadequacy of the perphenazine dose as a replacement of the haloperidol dose. In this case, the most plausible explanation is that the worsening of psychosis was a direct effect of the increase of clozapine levels associated with the addition of perphenazine. The worsening of psychosis was accompanied by the doubling of the clozapine levels along with myoclonus and hypersalivation (which are thought to be dose-related side effects). However, it is impossible to completely rule out the alternative explanations. The central message of this case is that a paradoxical worsening of symptoms can be the result of a drug-drug interaction of the medications used to treat the disease.

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