Letters to the Editor

Correction

Sir: In the recent article by Peterson and Cohen,[1] there is conflicting and inconsistent dosing advice for clonidine in Tourette's syndrome on page 68. The authors recommend starting clonidine at 0.25 mg once or twice daily and working up slowly to a total of 0.1 to 0.3 mg/day in 3 or 4 divided doses. First, clonidine comes only as unscored tablets of 0.1, 0.2, and 0.3 mg, so 0.25 mg is not a reasonable dose. Second, the titration schedule ends with a total daily dose less than the starting dose. Third, none of these doses can be divided by 4, and only 0.3 mg by 3. The PDR's advice for hypertension is to start at 0.1 mg twice daily and titrate to 0.3 mg b.i.d. Doses of up to 2.4 mg/day in divided doses have been used but are not recommended. Do the authors mean "0.1 to 0.3 mg 3 or 4 times daily," equating to a total daily dose of 0.3 to 1.2 mg?

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Drs. Peterson and Cohen Reply

Sir: We are grateful to Dr. Holmes for providing us with this opportunity to correct the typographical error that prompted his questions. Rather than starting clonidine at a dosage of "0.25 mg once or twice daily," the text should have read "0.025 mg." We hope that the next phrase ("and work up slowly to a total of 0.1 to 0.3 mg per day") will indicate the correct starting dose to the readers.

Dr. Holmes correctly notes that the 0.1-mg tablets (the smallest dose available) are unscored, which unfortunately can make the 0.025-mg dose (1/4 tablet) difficult to administer. Fortunately, precision is rarely necessary, since administering the remaining portions of the pill at subsequent doses compensates for what is lost or gained on any preceding single dose. The motivation for administering these small doses and titrating in small increments is to avoid the sedative side effects to which children are especially susceptible.

Instead of breaking the tiny 0.1-mg clonidine tablet to titrate the dosage upward, some clinicians advocate the use of the clonidine patch. While this seems like an attractive idea, in practice we have found that the patch is generally not well tolerated by children. It can be stigmatizing when noticed by peers, and for active children and in hot weather, it can fall off. In addition, the adhesives can produce local skin irritation and rashes. Finally, the clinical efficacy of the patch for treating tics seems typically to last 4 to 5 days, rather than the 7 days that the package insert indicates.

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Manic and Psychotic Symptoms Following Risperidone Withdrawal in a Schizophrenic Patient

Sir: Risperidone, a serotonin-2/dopamine-2 ($5HT_2/D_2$) receptor antagonist, has been demonstrated to be effective in reducing both positive and negative symptoms of schizophrenia.[1,2] Concerning its withdrawal-related symptoms, only akathisia[3] and dyskinesia[4] have been reported. In contrast, rapid discontinuation of clozapine, another atypical antipsychotic agent, could cause various symptoms including conscious disturbance, rebound psychosis, dyskinesia, motor restlessness, anxiety, insomnia, nausea, and diaphoresis.[5] We now present a chronic schizophrenic patient, who developed manic as well as psychotic symptoms upon risperidone discontinuation.

Case report. Mr. A, a 38-year-old Chinese man, was physically healthy and had never abused substances, including alcohol. He had a 19-year history of schizophrenia, but had never experienced manic or depressive episodes in the past. Four classes of traditional antipsychotics had failed to demonstrate significant efficacy. Taking haloperidol (5 mg/day) alone, he was recently admitted for acute exacerbation (earlier, higher dosages up to 20 mg/day yielded not better response but tremor and bradykinesia). Both positive (auditory hallucinations and persecutory delusions) and negative (avolition, affective flattening, and anhedonia) symptoms were evident. A thorough workup, including routine urine and blood laboratory tests, drug screening, electrocardiogram (ECG), and electroencephalogram (EEG), revealed negative findings. After a 3-day drug-free period, risperidone monotherapy was started at 1 mg b.i.d. and titrated to 2 mg b.i.d. on day 2. Sinus tachycardia, tremor, and akathisia ensued. Hence the dosage was tapered to 1 mg b.i.d. over 1 week. The adverse events vanished, and both positive and negative symptoms receded much after 6 more days. Mr. A was discharged following another 2 weeks, with the same dosage maintained. No other agents were coadministered since the initiation of risperidone.

Three days later, Mr. A lost his medicine accidentally. After 2 more days, auditory hallucinations and persecutory delusions recurred. Meanwhile, vivid manic symptoms (such as elevated mood, irritability, decreased need for sleep, hyperactivity, pressured speech, flight of ideas, and grandiosity) emerged for the first time throughout the history of his illness. Mr. A was thus

rehospitalized 3 days later. Complete examinations were repeated, providing normal results. Risperidone monotherapy (1 mg b.i.d.) was reinstituted and diminished both manic and psychotic symptoms within 5 days. Under this regimen, Mr. A has now been euthymic and with merely residual symptoms for 12 months.

This case suggests that psychotic and even manic features may arise with discontinuation of risperidone in certain patients; reinstitution could curtail the possible withdrawal reactions, perhaps within several days. Previous data have suggested that risperidone may have antimanic[1,6] or mania-inducing (or antidepressant) properties,[7–11] in addition to yielding antipsychotic effects. The unique pharmacologic characteristics of risperidone may account for its diverse activities.[6,11] Since risperidone therapy could modulate mood states, it is theoretically possible that its cessation might also alter moods in some individuals. Certainly, the above observations and hypotheses are preliminary. Further studies are warranted.

Another striking aspect of this case is the fact that this patient responded to 2-week risperidone monotherapy after 19 years of resistance to other classic agents. In accordance, a recent controlled double-blind, short-term (8-week) study[12] demonstrated that risperidone was as effective as medium-dose clozapine in 86 chronic schizophrenic patients who had been resistant to or intolerant of conventional neuroleptics. Risperidone, however, appeared to have a faster onset of action than clozapine.[12] Long-term trials in larger study groups are needed for confirming the effects of risperidone on treatment-resistant schizophrenia.[12]

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Treatment of Venlafaxine Discontinuation Symptoms With Ondansetron

Sir: Discontinuation symptoms that emerge during sudden or gradual discontinuation of serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, have been reported.[1] The short half-life of 5 hours for venlafaxine renders patients vulnerable to nausea, headache, gastric upset, diarrhea, myalgia, and fatigue upon lowering of the dosage. The manufacturer recommends a gradual discontinuation of venlafaxine to avoid the emergence of such symptoms.[2] However, even when such precautions are taken, symptoms may emerge. These symptoms can be relieved by using a cross-tapering strategy with the serotonin-3 (5-HT$_3$) receptor antagonist ondansetron, a medication more commonly used for the treatment of nausea and vomiting during radiotherapy and chemotherapy. The following case describes a patient whose somatic symptoms, believed to be caused by venlafaxine discontinuation, were managed by the addition of ondansetron.

Case report. Ms. A, a 29-year-old woman with a 12-year history of bipolar I disorder, had suffered from rapid cycling for the 3 years prior to seeking treatment. A combination of lithium and divalproex sodium eventually controlled daily mood shifts, but left her with residual and persistent depression. A trial of venlafaxine was attempted. Ms. A reached a dose of 150 mg PO b.i.d. and was maintained at that dose for 10 weeks without response. A tapering schedule was instituted by decreasing the venlafaxine dose by 37.5 mg every 3 to 4 days. Twenty-four days later, Ms. A had without difficulty reached a venlafaxine dose of 37.5 mg PO b.i.d. However, this proved to be a dose below which the tapering schedule could not be continued.

When receiving less than 75 mg/day of venlafaxine, Ms. A would experience nausea, headaches, diarrhea, and anxiety so severe that she was forced to remain at home. These symptoms would disappear when the venlafaxine dose was restored to 75 mg/day. Discontinuation symptoms remained unchanged even when the rate of dose diminution was reduced to 18.75 mg every 5 days. Ms. A continued taking venlafaxine, 37.5 mg PO b.i.d.; however, 4 mg b.i.d. to t.i.d. of ondansetron was added according to the severity of the discontinuation symptoms. This approach enabled Ms. A to decrease the dosage of venlafaxine by 18.75 mg every 3 or 4 days. The only side effect with ondansetron was constipation, which was easily treated with laxatives. Ms. A discontinued venlafaxine after 16 days. She then decreased the dose of ondansetron by 4-mg increments every 3 or 4 days. The discontinuation symptoms did not recur after she stopped ondansetron treatment.

Venlafaxine discontinuation symptoms are likely produced by the decreased inhibition of norepinephrine and serotonin reuptake mechanisms as the dose is decreased.[3] In the lower daily dose range (18.25–75 mg), venlafaxine blocks the reuptake of serotonin more than the reuptake of norepinephrine.[3] During long-term administration of a serotonin reuptake blocker, the number of 5-HT$_{1A}$ presynaptic receptors is thought to decrease at somatodendritic sites on serotonin neurons in the raphe nuclei.[3] Decreasing the daily dose below 75 mg gradually removes the blockade of the serotonin transporter, lowers the concentration of serotonin at these 5-HT$_{1A}$ presynaptic receptors, and increases the excitability of serotonin neurons, which in turn leads to increased availability of serotonin to act at receptors on postsynaptic neurons. It is this rise in excitability of serotonin neurons, and the resulting enhanced exocytosis of se-

rotonin onto postsynaptic neuron receptors, that is thought to produce discontinuation symptoms.

In Ms. A, the 5-HT$_3$ antagonist ondansetron relieved the nausea, headaches, gastric upset, and diarrhea, but did not significantly affect the anxiety. It is plausible that ondansetron relieved the nausea and headache by acting at central 5-HT$_3$ receptors, whereas it relieved the gastric upset and diarrhea by acting at gastrointestinal 5-HT$_3$ receptors.[4] The absence of anxiolytic effect by ondansetron suggests the involvement in the manifestation of discontinuation symptoms of other postsynaptic serotonin receptors unaffected by ondansetron, likely 5-HT$_2$.

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Fulminant Hepatic Failure From Acetaminophen in an Anorexic Patient Treated With Carbamazepine

Sir: We report a case in which a low overdose of acetaminophen resulted in hepatic failure requiring liver transplantation. We hypothesize that the severity of this patient's reaction was caused by the effects of an ongoing eating disorder in combination with the use of carbamazepine for treatment of a mood disorder, acting in a synergistic manner to magnify the toxic effects of acetaminophen. The association between eating disorders, carbamazepine, and acetaminophen overdose is discussed, an association that highlights the importance of evaluating disordered behaviors, as well as coadministered medications, in order to predict the severity of response to acetaminophen overdose.

Case report. Ms. A, a 17-year-old adolescent girl, presented to an emergency room 36 hours after reportedly ingesting 7800 mg of acetaminophen in a suicide attempt. Her past psychiatric history included a 4-year history of anorexia nervosa, binge eating/purging type, and borderline personality disorder. During the previous 2 years, she had multiple psychiatric hospitalizations for low weight. At the time of overdose, Ms. A's eating pattern had stabilized, and she was purging approximately 3 times per week. She had been amenorrheic for 4 years. Her weight was 98 pounds, and her height was 61 inches. For the past 6 months, Ms. A had been treated with carbamazepine, 100 mg in the morning and 200 mg at night, for mood stabilization. She denied any history of alcohol or drug abuse. The remainder of her medical history was unremarkable except for peptic ulcer disease.

At admission, Ms. A complained of abdominal pain, feeling ill, and vomiting, and she appeared sluggish. Abnormal laboratory values included a serum urea nitrogen of 132 mg/dL, a creatinine level of 1.6 mg/dL, and a serum glucose level of 179 mg/dL. Liver function test results were significantly elevated,

with a peak aspartate aminotransferase level of greater than 20,000 IU/L, a serum alanine aminotransferase level of 10,557 IU/L, a total serum bilirubin level of 3.3 mg/dL with a direct bilirubin level of 3.0 mg/dL, a serum alkaline phosphatase level of 223 IU/L, and a serum lactate dehydrogenase level of 42,805 IU/L. The peak serum albumin level was 4.4 g/dL, ammonia was 124 g/dL, and prothrombin time was 46.5 seconds. The serum acetaminophen level was 15 µg/mL. Ms. A was treated with acetylcysteine in the routine fashion, after which the serum acetaminophen concentration decreased at the expected rate.

Ms. A subsequently developed hepatic failure, and 8 days after her overdose she underwent liver transplantation. The pathology report of the excised liver revealed "subtotal central lobular hepatonecrosis with degenerative changes and severe cholestasis, compatible with acetaminophen overdose."

To our knowledge, this case presents the lowest dose of acetaminophen resulting in fulminant liver failure reported to date. The sensitivity of Ms. A to the toxic effects of acetaminophen can be explained by a combination of low body weight, malnutrition, and treatment with carbamazepine.

Acetaminophen is primarily metabolized to the sulfate or glucuronide conjugate. A small portion is metabolized by the cytochrome P450 mixed oxidase system to toxic metabolites, which are then detoxified by glutathione. Hepatonecrosis occurs when the glutathione stores are depleted and abnormally elevated levels of toxic metabolites accumulate. Doses of acetaminophen as low as 7500 mg have been shown to cause transient hepatotoxicity.[1] Carbamazepine[2–5] and fasting[6] are known to induce the cytochrome P450 mixed oxidase system. Diets low in protein result in decreased glutathione concentrations and increase the toxicity of acetaminophen.[7] Because Ms. A was treated with carbamazepine, the P450 mixed oxidase system was accelerated, and because of malnourishment, her glutathione stores were depleted, resulting in greater concentrations of toxic metabolites. These combined factors made Ms. A extremely sensitive to the toxic effects of acetaminophen. This case highlights the morbidity associated with this combination and the importance of considering behavior associated with psychiatric illness as well as the medication regimen in patients presenting with acetaminophen overdose.

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Movement Disorders and Psychotic Symptoms Treated With Pyridoxine: A Case Report

Sir: Neuroleptic-induced tardive dyskinesia continues to be a serious problem in the psychopharmacology of mental disorder.[1,2] The prevalence of tardive dyskinesia is approximately 24% among patients who are treated with neuroleptics for more than 1 year. The annual incidence in younger adults is 4% to 5%.[1,2] A large number of classes of medication have been studied in tardive dyskinesia patients, but no satisfactory treatment of the disorder is available.

Supersensitivity of striatal dopamine receptors was previously thought to be the mechanism involved in the development of tardive dyskinesia. It seems now that several neurotransmitter systems may be affected. These include dopaminergic, noradrenergic, GABAergic, cholinergic, and peptidergic pathways.[1] In addition, there is enough evidence to suggest that the blocking of central serotonin receptors by neuroleptics may be responsible for the development of tardive dyskinesia.[1–4] Furthermore, tardive dyskinesia may be associated with diminished pineal melatonin secretion: it is known that neuroleptics inhibit melatonin synthesis, and melatonin secretion is reduced in schizophrenic patients.[5,6] Viswanathan et al.[7] found that pyridoxine (vitamin B$_6$) increases cerebral serotonin function and melatonin production in experimental animals. In addition, there are 3 case reports[8–10] of improvement in tardive dyskinesia symptoms and neuroleptic-induced parkinsonism together with ameliorated psychotic symptoms after treatment with pyridoxine. We present an additional case demonstrating beneficial effects of pyridoxine on movement disorders and psychotic behavior.

Case report. Mr. A, a 22-year-old single male student with chronic organic persecutory paranoid ideation and recurrent explosive attacks, was suffering from polymorphic involuntary movements. He was born with "blue" asphyxia and with hematoma of the head that resolved when he was 3 years of age. At 2 years of age, choreoathetoid movements appeared in his upper and lower extremities, along with squinting of the eyes, rubbing of the hands, gesturing and clumsy movements, motor aphasia, and poor expressive language. Mr. A has been receiving neuroleptic therapy (thioridazine, trifluoperazine) since the age of 7 because of explosive attacks and periodical persecutory paranoid ideation. Despite his symptoms, he functioned academically and eventually graduated from high school. He has been in special university education for 3 years.

Approximately 5 years ago, Mr. A started therapy with haloperidol, up to 25 mg/day, and trihexyphenidyl, up to 4 mg/day, which successfully controlled parkinsonian symptoms. Today, he still receives the same therapy. Two years ago, he showed new kinds of involuntary movements—blinking, movements of the forehead and eyebrows, tongue-thrusting, licking of lips, smacking, and chewing—that were diagnosed as tardive dyskinesia. Mr. A was evaluated with the Abnormal Involuntary Movement Scale (AIMS) and the Brief Psychiatric Rating Scale (BPRS) (0–6 rating). He scored 27 on items 1 to 7 of the AIMS and 49 (sum of the total scores) on the BPRS.

At that time, he began treatment with pyridoxine, 200 mg/day, without knowing what medicine he was taking and for what reason. No clinical symptoms of vitamin B$_6$ deficiency were found. (Mr. A lived with his family and ate at home.) His plasma pyridoxal phosphate level was 52 nmol/L (normal range, 35–100). Mr. A was assessed twice a week with the AIMS and the BPRS. After 5 days of pyridoxine therapy in conjunction with his current medication, he experienced a drastic reduction in the severity of all movement disorders (sum of items 1–7 = 9).

Additionally, there was marked improvement in his behavioral and psychotic signs: he showed reduction of severity and duration of explosive attacks, and encapsulation and disactualization of paranoid ideas (sum of the total scores on the BPRS = 23). The symptoms of tardive dyskinesia reappeared only slightly, during times of mental stress, without producing functional disability. The beneficial effect of pyridoxine persisted over an 8-month period, after which an attempt to discontinue the medicine resulted in a dramatic exacerbation of the psychotic, behavioral, and dyskinetic disorders within 2 days. Within 3 days of renewal of treatment with pyridoxine, Mr. A again showed quick and marked improvement in his mental state and movement disorders. No side effects were reported or observed during treatment with pyridoxine.

The mechanisms by which pyridoxine ameliorated the symptoms of movement disorders and psychotic symptoms in our patient are not clear. We found no data about the influence of vitamin B$_6$ on antipsychotic effect of neuroleptics. It is possible that the decrease in movement disorders after the addition of pyridoxine to his treatment was effected by reduction of emotional tension connected to psychotic and behavioral symptoms. It is known that pyridoxine deficiency is associated with significant reduction in brain serotonin concentrations.[11,12] Moreover, pyridoxine is converted in the body to pyridoxal phosphate, which serves as a cofactor for a wide variety of metabolic transformation.[13] In the nervous system, some pyridoxine-dependent enzymes are involved in the GABA shunt, an alternate oxidative pathway restricted to nervous tissue. At present, the chronic use of neuroleptics produces free radicals that have been implicated in a variety of neuropsychiatric conditions. There is evidence that radical-induced damage may be important in at least some cases of persistent tardive dyskinesia,[14] and we suppose that pyridoxine, taking part in oxidative reactions, can be used as treatment in tardive dyskinesia.

Successful treatment of tardive dyskinesia is a very difficult issue. There are many prior reports of single cases about improvement in tardive dyskinesia with a variety of nonblind treatments, which have failed when studied in double-blind fashion. This is a single case report, and a double-blind study with a statistically meaningful number of patients is necessary for drawing definitive conclusions. Further studies are needed to investigate the role of pyridoxine in the treatment of movement disorders and psychotic symptoms.

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Risperidone Monotherapy for Psychotic Depression Unresponsive to Other Treatments

Sir: Risperidone, an atypical antipsychotic agent, has been reported to yield acute antidepressant effects in certain patients with schizophrenia,[1–3] schizoaffective disorder,[3,4] or psychotic depression.[3,5] Furthermore, it has been demonstrated that adding risperidone to preexisting antidepressants can improve chronic depression.[6,7] However, it remains unclear whether risperidone alone is effective in treating psychotic depression resistant to other treatments; earlier reports concerning risperidone monotherapy for psychotic depression did not reveal subjects' previous treatment responses.[3,5] We describe a case of psychotic depression in which a patient responded to risperidone monotherapy after treatment failures with several other strategies.

Case report. Ms. A, a 33-year-old Chinese woman, was physically healthy and devoid of any substance abuse history. Sixteen months ago, she was admitted to our hospital suffering from her first major depressive episode, which was accompanied by mood-congruent psychotic features. Depressed moods, loss of interest, insomnia, decreased appetite, loss of energy, psychomotor retardation, feelings of hopelessness, feelings of worthlessness, suicidal ideation, suicide attempts, delusions of guilt, and auditory hallucinations were marked. Physical examinations, hematology profiles, biochemistry and endocrinology analyses, urinalysis, chest x-ray, electrocardiogram (ECG), and electroencephalogram (EEG) all produced negative findings. Ms. A was then treated with fluoxetine (titrated to 60 mg/day in 3 weeks) and flupenthixol (up to 18 mg/day in 2 weeks). After 6 weeks, her mental status worsened. Consequently, a regimen consisting of fluoxetine, 60 mg/day, trifluoperazine, 15 mg/day, and bilateral electroconvulsive therapy (3 times a week) was started. The psychotic features subsided within 5 weeks, but Ms. A's mood improved only partially. Thereafter, only fluoxetine (60 mg/day) was continued. Unfortunately, both psychotic and full-blown depressive symptoms recurred 7 weeks later.

After a 2-day washout period, risperidone monotherapy was initiated; the dose was titrated to 4 mg/day over 4 days. Psychotic as well as mood disturbances receded without emergence of side effects after a 1-week risperidone trial; hence Ms. A was discharged with the same regimen. She was euthymic and symptom-free for 8 months until she herself discontinued the medication. One month later, a second episode of psychotic depression occurred. After 2 more weeks, risperidone monotherapy (up to 4 mg/day) was reinstituted, curtailing both psychotic and mood symptoms in 1 week.

Noteworthily, because fluoxetine and its active metabolite, norfluoxetine, both have long elimination half-lives (ranging from 26 to 220 hours and from 77 to 235 hours, respectively),[8] the residual fluoxetine (after its discontinuation) may have augmented the efficacy of risperidone in this patient's first episode. Nevertheless, in the second episode, risperidone monotherapy (definitely without other agents) still brought prompt improvement. Therefore, the present case suggests that in certain individuals even risperidone alone can be efficacious in curtailing psychotic depression unresponsive to other treatment modalities. Both 5-HT$_2$ and α_2-adrenergic affinities of risperidone might contribute to its potential antidepressant effects.[4,9]

The above observations and hypotheses should be considered preliminary. Because risperidone possesses antipsychotic effects, potential antidepressant properties, and favorable side effect profiles, further studies to elucidate the potential role of risperidone (alone or with concomitant antidepressants) in the treatment of psychotic depression unresponsive to other treatments are warranted.

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