Letters to the Editor

Olanzapine-Induced Mania

TO THE EDITOR: We present the following case of possible olanzapine-induced mania.

Mr. A, a 44-year-old man with a diagnosis of paranoid schizophrenia, had been seen at a mental health center for 19 years. An author (M.J.F.) had treated the patient for the past 8 years. A chart review revealed symptoms consisting of auditory and visual hallucinations, looseness of associations, and blunted affect. A careful review of his record did not reveal any history of manic symptoms.

Mr. A's medication consisted of a regimen of fluphenazine decanoate every 2 weeks and fluphenazine hydrochloride and diphenhydramine at night. A trial of olanzapine was initiated to control treatment-unresponsive hallucinations and to minimize the risk of exacerbating his tardive dyskinesia. His fluphenazine hydrochloride dose was discontinued, and the fluphenazine decanoate dose was reduced to every 3 weeks. One month later, he developed euphoria with frequent laughter, lessened sleep, and a higher sex drive. During a 5-day hospitalization, Mr. A's olanzapine dose was increased to 20 mg at bedtime, and he was started on a regimen of valproic acid and clonazepam. His serum valproic acid level on the day of his discharge was 95.3 μg/ml. Shortly after discharge, he was arrested for disturbing the peace. While in a correctional facility, he was under constant surveillance and continued to receive his medication. Two weeks after his discharge from the hospital, Mr. A was laughing continuously and uncontrollably. He could not answer questions or follow commands because of the laughter. The police reported that he did not sleep at all because of his laughter and exhibited almost continuous masturbatory activity for several days. A decision was made to taper and discontinue his dose of olanzapine. His fluphenazine decanoate, valproic acid, and clonazepam doses were increased. The correctional facility then reported that his sleep returned to normal and his laughter and masturbatory activity decreased. One week later, Mr. A returned to his usual state. His affect was blunted, and he experienced auditory hallucinations. His speech was not spontaneous, and he did not display loose associations. On follow-up examination, the manic symptoms had not returned.

Olanzapine is an atypical antipsychotic agent with high binding affinity for serotonin 5-HT_2, dopamine D_2, muscarinic, α-adrenergic, and histaminergic receptors. Its activity profile shows an effect on both positive and negative symptoms of schizophrenia (1). Antipsychotic agents are also used in the treatment of mania (2), and recent case reports suggest that olanzapine may be effective as well (3). A careful review of the literature shows only one other case of possible olanzapine-induced mania or hypomania (4). This additional case suggests that in some patients, olanzapine may precipitate mania.

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Quinapril and Depression

TO THE EDITOR: We report the case of an elderly man who developed the symptoms of a major depressive episode following the initiation of oral quinapril, 10 mg/day. Quinapril is de-esterified to quinaprilat, which is an inhibitor of angiotensin-converting enzyme. Angiotensin-converting enzyme inhibitors such as enalapril and captopril have been implicated in significant mood changes and other mental effects. They may induce depression (1), mania (2), and psychosis (3) and have also been reported to improve depression, psychosis, and cognition (4, 5). To our knowledge, no such side effects have yet been reported for quinapril.

Mr. A, a 90-year-old single white man with a history of peripheral vascular disease and mild congestive heart failure, presented with lessened appetite, insomnia, anhedonia, lessened energy, and suicidal ideation. His symptoms had started a month before when he was started on a regimen of oral quinapril, 10 mg/day, and worsened over the 2 weeks before admission. His other medications, which were not altered during the period, included oral furosemide, 20 mg/day, and oral digoxin, 0.125 mg/day. There was no prior psychiatric history. He did not abuse alcohol or drugs. He had a BUN level of 34 mg/dl, a creatinine level of 1.2 mg/dl, and a digoxin level of 1.2 mg/ml. His thyrotropin level, total iron-binding capacity, B_{12} and folic acid levels, and VDRL test results were all normal. At admission, a mental status examination revealed a man who was alert, oriented, and cognitively intact. His speech was clear, coherent, and goal directed. His mood was depressed and his affect constricted. He reported anhedonia, lessened energy, middle insomnia, and lessened appetite. He had suicidal ideation without intent or plan. He was without psychotic symptoms.

Since the mood change began right after quinapril treatment was begun, the recommendation was made to dis-

continue it. Mr. A was given diltiazem treatment. He reported improvement in his mood in the first 48 hours. He gradually recovered and, by the fifth day, was back to his baseline symptoms. Following his discharge, he did not feel any anhedonia or discouragement about the future.

This case illustrates a mood disorder secondary to an angiotensin-converting enzyme inhibitor in a man who fulfilled the criteria for a major depression that was probably induced by quinapril. Physicians should be alert to the possibility that quinapril may be associated with the onset of a depressive disorder and that switching to a different class of antihypertensive, rather than adding antidepressant medication, may alleviate the problem.

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Risperidone Monotherapy for Mania and Depression

TO THE EDITOR: Recently, risperidone (alone or, mostly, in combination with other mood stabilizers) has been tried in the treatment of bipolar disorder (1, 2). Nevertheless, its effects on mood seem hardly predictable: it has antimanic effects in some patients (1, 2) but mania-inducing (or antidepressant) effects in others (2). We describe a patient with bipolar disorder in whom risperidone monotherapy exhibited marked efficacy for his sequential manic and depressive states.

Mr. A, a 27-year-old man of Chinese descent, was physically healthy and did not abuse substances. About 1 year ago, he was hospitalized for his first episode of DSM-IV psychotic mania. Elevated moods, lessened need for sleep, hyperactivity, pressured speech, flight of ideas, grandiosity, and visual, mood-congruent hallucinations significantly impaired various areas of functioning. Physical examinations, laboratory tests, drug screening, chest X-rays, an ECG, and an EEG all produced negative results. In addition, his elder brother was also a victim of bipolar disorder. Mr. A and his father gave written informed consent for him to receive risperidone monotherapy; his dose was titrated to 3 mg b.i.d. over 3 days. Both psychotic and mood symptoms vanished within 3 weeks; he was then transferred to our outpatient department with the same drug regimen.

Two weeks later, Mr. A abruptly discontinued his medication because of a lack of full insight; after 6 days, a less severe manic state (without psychotic features) returned. Five days later, risperidone alone (3 mg b.i.d.) was reinstituted, abating his mood turmoil over 1 week. Unfortunately, 1 month later, he again discontinued his medication; a DSM-IV major depressive episode with melancholic features ensued 1 week later. Distinct depressed moods, significant anorexia, early morning awakening, loss of energy, marked psychomotor retardation, loss of pleasure in all activities, excessive guilt, and feelings of hopelessness caused drastic distress. After another 2 weeks, the same monotherapy alleviated the depressive state within 1 week. Three weeks later, Mr. A halted the medicine for a third time. Thereafter, he was free of psychotic and mood symptoms for 9 months, until another major depressive episode (with similar symptoms) developed. Two weeks later, the earlier treatment strategy curtailed this episode over 1 week. No adverse drug reaction ever emerged; no other medication, even as an adjunct, was coadministered throughout.

To our knowledge, this is the first report of risperidone monotherapy for both manic and depressive episodes of bipolar disorder. Although Mr. A's mood fluctuation might merely reflect the natural course of his illness, the temporal relationship with risperidone's (re)initiation or suspension suggests otherwise. Rigorous studies are needed to examine this preliminary observation.

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Olanzapine-Induced Neuroleptic Malignant Syndrome With Mental Retardation

TO THE EDITOR: Neuroleptic malignant syndrome is a potentially lethal side effect of antipsychotic medication. It may occur in as many as 1% to 2% of patients treated with antipsychotic medication (1). Operational criteria include 1) fever (oral temperature greater than 37.5°C on two occasions); 2) extrapyramidal features, including one of a) moderately severe rigidity; b) at least two of mild rigidity, dysphagia, shuffling gait, resting tremor, dystonia, dyskinesia, and a creatinine kinase level greater than 400 U/liter; or c) a creatinine kinase level greater than 1000 U/liter; and 3) either a) altered consciousness or catatonia or b) autonomic instability (two or more of hypertension, labile blood pressure, tachycardia, intense diaphoresis, incontinence, and tachypnea) (2). Although most of the reported cases of neuroleptic malignant syndrome to date have been associated with the use of classical antipsychotics, both risperidone (3) and clozapine (4) have been implicated in the emergence of the syndrome. We report here the first case of neuroleptic malignant syndrome induced by the novel antipsychotic olanzapine that met these operational criteria.

Mr. A was a 21-year-old black man with mild to moderate mental retardation believed to be related to the menin-

gitis he suffered as a child. He had been treated for several years with low-dose haloperidol for behavioral difficulties and, as a result, suffered from abnormal dystonic and dyskinetic movements. On two previous occasions, he met the criteria for probable neuroleptic malignant syndrome, with creatinine kinase level elevations to 12,000 U/liter on one occasion and 1,000 to 2,000 on the other.

Mr. A's medication regimen consisted of clonazepam, 1 mg/day, benztropine mesylate, 1 mg/day, and lorazepam as needed because a trial of tetrabenazine had failed. He was then started on a regimen of olanzapine. The dose was gradually increased to 12.5 mg over a 12-day period, in which some decrease in agitation and improved behavior were noted. On day 13, Mr. A became extremely agitated and had an increase in abnormal movements as well as mild rigidity. Olanzapine was immediately discontinued. His rectal temperature rose to 40.6°C and was measured on another occasion as 40.2°C. His creatinine kinase level rose to 6030 U/liter (normal range=20–195), and his WBC count rose to 17.4×10^9/liter (normal range=4–11). Tachycardia (124 bpm) and hypertension (systolic pressure=150 mm Hg, diastolic pressure=100 mm Hg) were also recorded. These met the criteria for neuroleptic malignant syndrome (2).

We treated Mr. A with oral liquid diazepam to help control his extreme agitation, which appeared to be the predominant symptom, along with his dystonic and dyskinetic movements. We also administered dantrolene, 50 mg/day. His creatinine kinase level values had decreased to 393 U/liter by day 6 and had returned to near normal (208 U/liter) by day 8. Any attempt to decrease his dose of dantrolene resulted in an increase in his creatinine kinase level, his WBC count, and temperature. Mr. A had risk factors of extreme psychomotor agitation (5) and mental retardation (6). Our choice of treatment with oral liquid diazepam was indicated because of Mr. A's extreme agitation (7).

One should be alert to this serious side effect associated with atypical antipsychotic medication, including olanzapine.

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Improvement of Sleep and Behavior by Methylphenidate in Alzheimer's Disease

TO THE EDITOR: We present an interesting case of a patient with Alzheimer's disease whose insomnia, restlessness, and memory impairment responded to treatment with methylphenidate.

Mr. A, a 78-year-old white man, had a 4-year history of slow-onset, progressive dementia of the Alzheimer's type. As his dementia progressed, he would sleep no more than 1 or 2 hours per night, instead pacing or wandering around the house. When his wife could no longer manage him, she placed him in a long-term care dementia unit.

Upon hospitalization, Mr. A needed assistance with dressing, grooming, and bathing but could feed himself and walk independently. There was no history of alcohol consumption. There was a family history of Alzheimer's disease. He had non-insulin-dependent diabetes. Results of his examination were otherwise unremarkable and did not indicate the presence of Parkinson's disease.

In the unit, he continued to have insomnia and paced the halls at night. During the day, Mr. A would sit expressionless in a chair, not interacting with other patients or staff. After several medications were used unsuccessfully to treat his insomnia, Mr. A's sister mentioned that her son, who had attention deficit hyperactivity disorder (ADHD), had been treated with methylphenidate, which improved his insomnia. Methylphenidate is an indirect-acting sympathomimetic agent used to treat individuals with ADHD and narcolepsy and geriatric patients who are apathetic and withdrawn. It has been shown to reduce anger and temper outbursts, to improve memory in patients who have sustained head injury (1), and to improve attention, reduce impulsivity, decrease motor activity, and improve social behavior style.

Mr. A started taking methylphenidate, 5 mg b.i.d., which was increased to 10 mg b.i.d. after 2 days. He slept all night for the first time in 4 years. More remarkably, his facial expression and interaction with other patients and staff markedly improved. He started occupational therapy, kinesitherapy, horticulture therapy, and recreational therapy. His wife noticed that he could remember her visits from the previous day and was much more animated and interactive than she had seen him in years.

To test whether the sleep improvement was caused by the methylphenidate, we tapered and discontinued the drug. Mr. A's symptoms worsened, particularly insomnia and restlessness. His wife said that he was not as interactive as he had been before and could not remember her visits. Methylphenidate was restarted, and his symptoms once again improved. Whether Mr. A's improved activity and participation were directly related to methylphenidate or to improved sleep is unknown.

We conclude that stimulants should be considered, particularly for patients with Alzheimer's disease who may have a history of ADHD, for treating sleep disturbance and may be useful in reducing motor activity like pacing. We emphasize extreme caution in the use of this drug with Alzheimer's disease patients because it may cause agitation. Controlled trials with methylphenidate may be of interest, with a low starting dose and careful observation during the clinical trial.

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Possible Nefazodone Withdrawal Syndrome

TO THE EDITOR: We report a case of a possible withdrawal reaction following the discontinuation of nefazodone.

Mr. A was a 28-year-old white man who enrolled as a healthy volunteer in a study protocol conducted at our institution. Written informed consent was obtained from Mr. A after the study procedures were explained. The protocol required that subjects receive 9 days of nefazodone therapy. The dose was titrated over the course of 4 days to 200 mg twice daily. It was maintained for 5 days and then abruptly discontinued.

Mr. A complained of dizziness and "electrical sensations down [his] legs" beginning approximately 36 hours after his final nefazodone dose. The electrical sensations lasted throughout the night and were described as "tickling electrical sensation[s]" severe enough to interfere with sleep. The discomfort would subside upon movement but return after approximately 30 seconds of immobility. By the following morning (48 hours after nefazodone discontinuation), the leg symptoms had subsided. Dizziness, however, persisted throughout the day and at times led to nausea. Seventy-two hours after discontinuation, his dizziness had begun to subside and was completely gone shortly thereafter.

Although single doses of dextromethorphan and methylprednisolone were administered as study medications, they were unlikely to cause these symptoms. Mr. A reported that he had never experienced similar symptoms.

The possibility of a withdrawal reaction occurring after the discontinuation of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine has previously been documented (1). Withdrawal symptoms typically occur 24 to 72 hours after SSRI discontinuation and can include sensory disturbances (e.g., parasthesia, sensations of electric shock), gastrointestinal complaints, dizziness, flu-like symptoms, and sleep disturbances (2). The incidence of withdrawal symptoms may be inversely related to the SSRI's half-life, with fluoxetine having the lowest risk of a withdrawal reaction and paroxetine and fluvoxamine having the highest (1). However, symptom appearance could also be delayed in long half-life drugs, leading to underreporting for these agents.

The electric shock-like symptoms, dizziness, and nausea reported by Mr. A upon abrupt nefazodone discontinuation appear consistent with those reported by others to be typical of SSRI withdrawal. Nefazodone, like other SSRIs, is an inhibitor of serotonin reuptake. It is also an inhibitor of norepinephrine reuptake, a potent serotonin antagonist, and an α_1-adrenergic receptor antagonist (3). Because nefazodone has SSRI-like properties and a short half-life, it could possibly cause an SSRI-like withdrawal syndrome upon abrupt discontinuation.

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Treating Visual Hallucinations With Donepezil

TO THE EDITOR: The typical approach to the treatment of visual hallucinations has been to administer a drug with dopamine-blocking properties. We report the case of a patient with persistent visual hallucinations arising in the postoperative period who responded to the acetylcholinesterase inhibitor donepezil.

Mr. A was a 74-year-old married white man with a high school education who was referred by his internist for evaluation and treatment of visual hallucinations. He had been in good health before an operation for spinal stenosis several months previously. The operation had been successful in alleviating his lower extremity pain and weakness but left him with a new problem—persistent and disturbing visual hallucinations.

The hallucinations began in the postoperative period and were present during most of his waking hours. Shortly after the onset of the hallucinations, he was evaluated by a neurologist, who felt that the cause might be related in part to macular degeneration or an incipient dementia. At that time, a computerized tomography scan showed minimal atrophy, and an EEG demonstrated diffuse slowing without focal abnormality; his Mini-Mental State examination score was 25.

At our consultation, Mr. A was alert and pleasant, although somewhat embarrassed about discussing the hallucinations. However, once given the opportunity to freely talk about the phenomenon, he described his hallucinations vividly and with considerable affect. He reported seeing people in his living room and in the backseat of his car. He could not understand why these people were coming into his house and why they did not need to go to the bathroom or eat. He was not fearful but worried what the neighbors would say about "all this coming and going." These hallucinations were highly disturbing to his wife.

While he felt his memory was not as good as it once was, his wife said she had not observed any significant cognitive problems. He said that he did not have depressive symptoms, delusions, or hallucinations in any other modality. He scored 21 on a repeat Mini-Mental State examination, missing one item on orientation, recall, repetition, and copying and all of a three-stage command. There was no previous history of psychiatric illness. His mother had died in her late 80s of cancer and was "forgetful."

Given the isolated nature of the hallucinations, the desire to avoid use of a neuroleptic, and the emerging evidence that cholinergic therapy may be an effective treatment for visual hallucinations, a trial of donepezil, 5 mg at bedtime, was begun. Over the first 2 weeks, there was little change, but over the ensuing week, there was a fading of the hallucinations until, after 4 weeks, the hallucinations had entirely abated. Mr. A's dose was subsequently lowered to 5 mg every other day, with absence of the hallucinations for approximately a week. However, at that time, the hallucinations began to return but responded to reinstitution of a daily dose. It is interesting that his wife, who had adamantly denied that her husband had any memory problems at the initial evaluation, spontaneously asked "whether that drug is supposed to help memory," reporting that her husband seemed sharper overall.

This case demonstrates the potential of cholinesterase inhibitors to treat visual hallucinations, a symptom that often responds poorly to antipsychotics in the elderly (1). The etiology of Mr. A's visual hallucinations and their resolution are far from clear. He had features that may indicate an incipient degenerative dementia, potentially of the Alzheimer's or Lewy body type. A prolonged delirium is another possibility, with his variable cognition, hallucinations, and difficulty with some aspects of concentration. Charles Bonnett syndrome is another possibility, although Mr. A lacked insight into the nature of his hallucinations.

Cholinergic agents have been used successfully in treating acute delirium, and increasing evidence suggests that they may have a special role in treating visual hallucinations that occur with Alzheimer's disease (2–5). In theory, cholinergic agents should also be quite effective in Lewy body dementia, where the cholinergic deficit is profound (6). More systematic study of this relationship is warranted in view of the limited efficacy of antipsychotics and the more favorable side effect profile of donepezil.

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Olanzapine Overdose

TO THE EDITOR: Overdose experience with the newer second-generation antipsychotics, including olanzapine, is limited. However, concern for serious consequences is warranted considering the nanomolar affinities of these agents at receptors affecting cardiovascular and central nervous system functioning. We report a case of acute overdose with 1110 mg of olanzapine.

Ms. A was a 29-year-old, 98-kg, one-pack-per-day smoker with a diagnosis of schizophrenia for 13 years, presenting with auditory hallucinations, paranoia, and negative symptoms. A regimen of olanzapine had been started 6 weeks earlier; her current dose was 30 mg/day. On the day of admission and in response to a command hallucination, she swallowed the combined contents of new and partial prescriptions of olanzapine (111 10-mg tablets). Approximately 1 hour later, she informed her mother and was immediately taken to a local emergency room. Ms. A had a history of intermittent suicidal thinking and a remote history of one overdose.

On arrival, she was combative and agitated, tachycardic (147 bpm), and tachypnic (respiratory rate=28 breaths/minute), with a systolic blood pressure of 129 mm Hg and diastolic blood pressure of 69 mm Hg, and oxygen saturation of 88%. She was treated with activated charcoal and sorbitol and admitted to the intensive care unit overnight for monitoring. An ECG showed sinus tachycardia but was otherwise normal. Her blood pressure was variable (systolic=110–130 mm Hg, diastolic=60–90 mm Hg), and her heart rate decreased to 115 bpm overnight. There were no significant acid-base changes (pH=7.39, PCO_2=37 mm Hg, HCO_3=23 mmol/liter), but the partial oxygen pressure was 55 mm Hg. Oxygen saturation remained above 90%, avoiding the need for oxygen treatment. Normal intravenous saline solution was given at 150 ml/hour overnight. The results of CBC, electrolyte, liver enzyme, and thyroid-stimulating hormone tests were essentially within normal limits. Overnight, Ms. A was drowsy, napping, mumbling when awakened, and incontinent of urine once.

The following morning, Ms. A's blood pressure was 130/92 mm Hg, and her ECG was normal with the exception of sinus tachycardia (105 bpm). She was oriented, pleasant, and not regretful of overdosing and remained delusional. Eleven hours after admission to the intensive care unit, she was medically stable and was transferred to the mental health unit, where she was treated with clozapine and discharged approximately 4 weeks later. No psychotropic medications were given in the emergency room or intensive care unit.

In the first year of marketing, 72 single-drug overdoses that involved olanzapine were reported to Eli Lilly and Co., the manufacturer, 60 with known quantities ingested (40–1125 mg). Among these were two deaths apparently caused by olanzapine, one of which was reported (1; C. Beasley, Eli Lilly, personal communication, June 10, 1998). Postmortem blood concentrations of the drug were high, 40 to 200 times greater than mean therapeutic plasma concentrations.

We report a large overdose involving olanzapine alone that was associated with tachypnia, sinus tachycardia, fluctuating blood pressure, and brief hypoxemia. However, respiratory and cardiovascular function returned to normal within 16 hours of ingestion with minimal interventions. Ms. A's rapid

recovery may reflect the early administration of activated charcoal, which has been shown to decrease the oral bioavailability of olanzapine by 50% to 60%, according to the manufacturer.

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Amiodarone-Induced Delirium

TO THE EDITOR: Amiodarone is a class III antiarrhythmic with neurologic toxicity, but there have been rarely reported psychiatric disturbances. The English literature contains one other case report of amiodarone-induced delirium (1).

Mr. A was a 54-year-old man with a history of idiopathic cardiomyopathy and congestive heart failure with ventricular tachycardia who was admitted for worsening congestive heart failure and a new onset of atrial fibrillation. He was discharged 4 days later on a new drug regimen that included bumetanide, 4 mg b.i.d., enalapril, 20 mg b.i.d., and amiodarone, 400 mg b.i.d. Four days after his discharge, Mr. A's wife reported that he was experiencing mental status changes consisting of depression, paranoia, lessened sleep, and rambling speech. After 3 days of persistent altered mental status, she brought him to the emergency department. Mr. A was evaluated and sent home with a lower dose of amiodarone (200 mg b.i.d.). His mental status and ability to sleep initially improved but distinctly worsened 3 days later.

Mr. A was subsequently admitted to the psychiatry service with confusion, tangential thinking, labile affect, and a new macular rash on his extremities. Laboratory test results were normal except for a serum sodium level of 127 meq/liter and a BUN of 35 mg/dl. The results of a computerized tomographic scan of the head were normal. Mr. A had no previous psychiatric history. All drugs were discontinued, and he received 2 mg each of haloperidol and lorazepam.

On the fourth hospital day, he was alert and oriented with good memory and concentration, and the rash noted on admission had disappeared. However, on this same day, he was transferred to the cardiac critical care unit with worsening congestive heart failure, renal dysfunction, and a serum potassium level of 6.9 meq/liter, a creatinine level of 1.8 mg/dl, and a sodium level of 126 meq/liter.

After 5 days in the cardiac critical care unit (his ninth hospital day), Mr. A resumed taking amiodarone, 200 mg/day, for worsening atrial fibrillation. No other medications were added. Mr. A received 3 days of amiodarone treatment, and on the fourth day, he was noted to be increasingly agitated, confused, and paranoid. He was subsequently treated with haloperidol. Four days after discontinuing the amiodarone, Mr. A returned once again to his baseline normal mental status. Laboratory values and cardiac perfusion remained abnormal, but no further mental status changes occurred. On hospital day 22, Mr. A died because of progressive heart failure.

Neurologic toxicity with amiodarone has been reported (2). Mr. A had a more rapid onset of delirium than the patient reported by Trohman et al. (1), but his symptoms subsided within a similar time frame, both initially and upon rechallenge. This variability may be explained by the drug's large volume of distribution and its elimination half-life of 26 to 100 days.

Other diagnoses contributing to mental status changes could not be completely ruled out. However, the temporal relationship between Mr. A's amiodarone use and the onset and resolution of delirium is compelling.

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Clozapine for Substance-Abusing Schizophrenic Patients

TO THE EDITOR: Substance abuse, including cocaine, is common among individuals with schizophrenia (1). While effective medications for these dual-diagnosis patients have not been established, atypical antipsychotics may hold promise. Clozapine has been reported to decrease alcohol and cocaine use in chronically psychotic patients (2). Other atypical agents may also be effective in reducing cocaine use as well (unpublished report by J.W. Tsuang et al., 1998). This report describes a patient who stopped abusing drugs when treated with clozapine.

Mr. A, a 43-year-old single white man with a 15-year history of paranoid schizophrenia and cocaine and alcohol abuse, had been hospitalized more than 20 times as a result of psychotic exacerbations concurrent with drug and alcohol abuse. He underwent multiple medication trials without any significant change. Mr. A used alcohol and cocaine intermittently, despite participating in our dual-diagnosis treatment program. Although he was medication compliant, his psychotic symptoms persisted. He was treated with clozapine, and the dose was gradually increased to 550 mg/day at bedtime. Since then, he has had no further hospital admissions. His memory has improved, and he is able to use skills from the drug-relapse classes. He has had no medication side effects, and he reports that he only has occasional psychotic symptoms. Mr. A has not used alcohol or cocaine since starting clozapine treatment, as validated by weekly urine analyses. Moreover, he claims that his cravings for drugs and alcohol have been reduced by clozapine, and when these cravings do occur, they are often easier to manage. Currently, he remains abstinent, and he is psychiatrically stable.

Mr. A's case, and others that we have treated, suggests that clozapine may reduce substance abuse while decreasing psychotic symptoms in chronically ill schizophrenic patients. Although the reasons are uncertain, a lesser need to self-medicate psychiatric symptoms and greater insight into the negative consequences of drug use are possible explana-

tions. Furthermore, it has been proposed that higher dopamine concentrations and additional serotonergic input are required for psychostimulant-induced euphoria (3). Sole manipulation of the dopamine system to reduce cocaine use has not been effective (3). Using clozapine to block serotonin receptors might reduce cravings and the euphoric effects of cocaine. Additionally, atypical agents are less disruptive to cognitive functions, thus enabling the use of coping skills learned during treatment. We are currently conducting trials to determine whether atypical agents are more effective for dual-diagnosis patients.

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Depression From Interferon Therapy in Patients With Hepatitis C

TO THE EDITOR: The number of patients treated with interferon therapy has increased markedly in Japan since 1992, when the Health and Welfare Ministry approved the use of interferon for treating chronic active hepatitis C. Since then, there have been some case reports of severe depression and suicide among patients during interferon therapy. However, the incidence of depression is still not known. We report on the incidence of and risk factors for depression among hepatitis C patients receiving interferon therapy, on the basis of a prospective follow-up study.

All of the 66 patients (25 women and 41 men; mean age=49.9 years) with hepatitis C who began receiving interferon therapy at Showa University Hospital from December 1992 to December 1993 gave informed consent for participation in this study and were investigated prospectively. Recombinant interferon-alpha-2b was administered to 33, natural lymphoblastic interferon-alpha to 29, and other forms of interferon to four of these patients. Ten million units of recombinant interferon-alpha-2b or 6 million units of natural lymphoblastic interferon-alpha were given to patients intramuscularly every day for the first 2 weeks and then three times a week for the next 22 weeks. The patients were hospitalized for the first 4 weeks, with subsequent treatment at an outpatient clinic for the next 20 weeks. Psychiatric assessments were performed four times (before the treatment [at 0 weeks] and at 4, 12, and 24 weeks) by a psychiatrist (T.O.).

Interferon therapy was discontinued in three cases because of physical side effects and in four cases because of severe depression (two cases at 7 weeks, one at 9 weeks, and one at 20 weeks). The numbers of patients whose symptoms satisfied the criteria for major depressive episode in DSM-III-R were three of 66 (4.5%), 14 of 64 (21.9%), 23 of 60 (38.3%), and 16 of 59 (27.1%) at 0, 4, 12, and 24 weeks, respectively. Twenty-nine patients were not depressed before the treatment but were diagnosed with depression at least once during interferon therapy. The mean maximum Hamilton Rating Scale for Depression score among the four assessments in these 29 patients was 20.5 (SD=5.7). Two of these patients had suicidal ideation, but neither attempted suicide. Thirty-one patients completed the 6-month course of interferon therapy without experiencing depression. There were no significant differences between the groups that did and did not experience depression during interferon therapy in sex (15 men and 14 women versus 22 men and 9 women) and age (50.0 versus 49.6 years). The mean Hamilton depression scale score at week 0 was significantly higher in the 29 depressed patients (3.5) than in the 31 undepressed patients (2.0) (Wilcoxon rank sum test, $p<0.05$).

The depressed patients in this study were definitively diagnosed as having a psychoactive substance mood disorder, an organic mood disorder, or major depression because it is unclear whether the neurotoxicity of interferon therapy exclusively causes depression. Our findings indicate that careful monitoring for symptoms of depression in patients receiving interferon therapy is required.

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Smoking in First-Episode Patients With Schizophrenia

TO THE EDITOR: Patients with chronic schizophrenia smoke at substantially higher prevalence rates (70%–80%) than the general population (25%–30%) (1, 2). Reasons suggested to explain this include the following: 1) smoking lowers antipsychotic blood levels (and extrapyramidal side effects [2]) by stimulating hepatic microsomal enzymes (3), and 2) nicotine reverses antipsychotic-induced cognitive slowing (4). However, there is also evidence that smoking produces direct "therapeutic" effects (i.e., independent of its interactions with antipsychotics) for patients with schizophrenia. For example, nicotine corrects abnormalities in sensory gating seen in many patients with schizophrenia and in 50% of their first-degree relatives (5).

If patients with schizophrenia smoke primarily to reverse the effects of antipsychotic drugs, those with chronic schizophrenia should smoke at substantially higher prevalence rates than first-episode patients.

We interviewed and observed 22 consecutively admitted, first-episode patients with schizophrenia or schizophreniform disorder; all patients gave written informed consent after the procedures were explained to them. The patients had less than 30 days' previous lifetime exposure to antipsychotics; 17 (77%) smoked. Twelve of these 22 patients had no previous exposure to antipsychotics; 11 of these 12 (92%) smoked.

The fact that first-episode patients smoke at the same prevalence rate as chronic patients suggests that it is schizophrenia, not its treatment with antipsychotic drugs, that determines this prevalence. Pharmacologic agents with therapeutic

effects on nicotine-sensitive pathophysiologic mechanisms in schizophrenia may decrease a patient's drive to smoke and reduce the associated health risks.

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Clozapine to Olanzapine

TO THE EDITOR: The role of olanzapine in the treatment of severe refractory schizophrenia is unclear. We report our experience in switching five men with refractory schizophrenia and self-induced water intoxication from clozapine to olanzapine.

We stabilized five men with a regimen of clozapine, but they were still too ill to be released from the hospital. We hoped they would have a better response to olanzapine. Their mean age was 40.8 years. Their mean current hospital stay was 13.6 years. The patients were all on a specialized ward for the treatment of self-induced water intoxication. All patients initially had a clozapine blood level greater than 360 ng/ml. One patient also received lithium, and another took valproic acid as an adjuvant to clozapine.

We increased their olanzapine dose and tapered their clozapine dose over a 3-week period. Their mean maximum olanzapine dose was 24 mg/day (range=20–25 mg/day). We obtained an olanzapine blood level on each patient to ensure compliance. We did not alter adjuvant medications. The Positive and Negative Syndrome Scale for Schizophrenia (PANSS) was completed by a psychologist before the start of olanzapine and again after 4 months of treatment or at discontinuation, if this occurred earlier.

We had to discontinue olanzapine in two patients after 2 months when they developed rage attacks. We took two other patients off of olanzapine after 4 months when their psychotic symptoms markedly increased. We left one patient taking olanzapine, because clinically he was unchanged from when he was taking clozapine. The mean PANSS score for the five patients increased from 91.4 to 125.8 (paired t test= 2.74, df=4, p=0.05).

The fluid consumption of the five patients, as assessed by weight monitoring, did not increase significantly with olanzapine treatment. As a consequence, the clinical deterioration of the four patients resulted directly from an exacerbation of their schizophrenia rather than through a worsening of their self-induced water intoxication.

On the basis of this open-label study of refractory schizophrenic patients with self-induced water intoxication who were only partially responsive to clozapine, switching from clozapine to olanzapine may not be helpful.

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Psychopharmacologic Calvinism

TO THE EDITOR: Poor John Calvin! In two different recent educational audio programs, eminent psychiatrists use Calvin's name in decidedly pejorative ways. In an audiograph series of the *Journal of Clinical Psychiatry* (1), Sumer D. Verma, M.D., states that "we have this Calvinistic view about treating pain in the long-term care setting: 'We must not give them too much analgesia because—you never know—Grandma might become addicted.'" Being fairly sure that Calvin never directly addressed the issue of treating pain with analgesics, I have to speculate about Dr. Verma's use of "Calvinistic." He seems to suggest that Calvinists are so fearful of the potential evil consequence of analgesia (addiction) that they miss the greater good (pain relief). I do not think he means to imply that Calvinists, with their strong view of God's sovereignty, find purpose in their suffering and therefore tend to forgo analgesia. Nor does he seem to mean, thankfully, that Calvinists sadistically wish people to suffer. However, he does imply a certain narrow, joyless way of thinking that can be summarized as "what you like isn't good for you, and what you don't like is good for you."

This is, in fact, Thomas Gutheil's definition of "psychopharmacologic Calvinism" (2), which he discusses in a lecture distributed on a recent edition of the Audio-Digest tape series. He applies the phrase to patients with borderline personality disorder who tend to desire substances with which they do not improve (alcohol, street drugs, and benzodiazepines) and improve with drugs that they do not like (lithium, monoamine oxidase inhibitors, phenothiazines). Like Verma, Gutheil posits denial as central to Calvinism. Unlike Verma, Gutheil suggests that this form of Calvinism—psychopharmacologic Calvinism—is, in fact, good psychiatric practice, whereas Verma's "analgesic Calvinism" is denounced as inappropriate.

Seemingly, these two psychiatrists are ascribing to Calvin incompatible views. However, in both formulations, the emphasis is on the patient's perspective—namely, the denial of that which is desired. Despite Gutheil's endorsement of the clinical practice, he jokingly invokes Calvin's name to label a way of thinking in which people's desires are ignored—namely, a rigid, mindless, killjoy denial. Thus, despite superficial appearances, these views reflect a similar view of Calvinism as a grim theology.

A brief examination of Calvin's thoughts may help paint a more accurate picture of his theology. Calvin certainly does enjoin Christians to face "all the accidents to which this present life is liable," whether disease, pestilence, or the calamities of war, "with patience and endurance" (3). This attitude is to be rooted in an understanding of God as the "ruler and arbiter of the fortunes of all" (3). While the individual is enjoined to adopt this attitude toward his own situation, the Christian's attitude toward others is to be characterized by a charity derived from the recognition that man "is distinguished by the lustre of his [God's] own image" (3). This recognition, Calvin asserts, should lead Christians to "put themselves in the place of him whom they see in need of their assistance," which should then "incline him to assist

him" (3). Further, Calvin condemns excessive austerity characterized by the belief that "earthly blessings" are to be used only for necessities and not for pleasure (3). Such a view, he contends, "not only maliciously deprives us of the lawful fruit of the divine beneficence, but cannot be realized without depriving man of all his senses, and reducing him to a block" (3).

While Calvin admonishes believers not to curse God for their present misfortunes, he does not advocate ignoring the suffering of others. Nor does he commend a joyless, grim life in which suffering is pursued. When psychiatrists such as Gutheil and Verma use "Calvinistic" in the erroneously simplistic manner cited previously, they do not do justice to the richness of Calvin's theology. Sadly, this use seems to reflect American psychiatry's ignorance of theology and its import. This ignorance can only further exacerbate the wariness and skepticism toward psychiatry felt by many people of faith.

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Valproate for Alcoholics With Bipolar Disorder

TO THE EDITOR: Valproate was recently approved by the Food and Drug Administration for the treatment of acute mania associated with bipolar disorder. A rare and potentially fatal complication from valproate therapy is hepatotoxicity (1). This complication may be especially important in alcoholics because of the risk of preexisting liver disease as a result of excessive alcohol consumption. Additionally, chronic alcohol use may cause lower white blood cell and platelet counts, which may also complicate the use of valproate with alcoholics. We report on liver function as well as platelet and white blood cell counts in 20 patients with bipolar disorder and alcoholism who received valproate therapy for as long as 2 years.

The charts of 20 patients (12 men and eight women) with comorbid bipolar disorder and alcohol abuse/dependence who had been prescribed valproate were reviewed, and results of the following laboratory tests were evaluated: alkaline phosphatase, alanine aminotransferase, lactate dehydrogenase, γ-glutamyltransferase, aspartate aminotransferase, total bilirubin, WBC count, and platelet count. All patients had baseline test results and at least one set of follow-up laboratory test results for comparison. The patients were followed for an average of 5 months. Their average age was 38.7 years (SD=8.5). The patients had an average valproate level of 69.9 mg/liter (SD=15.8), with an average daily dose of 1562.5 mg (SD=499.1).

Laboratory test results were divided among the following time frames for comparison: baseline, less than 2 months after valproate treatment was started, 2 to 8 months, and more than 8 months. All laboratory test results were within normal range at baseline except the γ-glutamyltransferase. There were no statistically significant changes from baseline test results for any of the liver transaminases or the WBC count. There was a statistically significant decrease in platelet count from an average of $286.6\times10^3/\mu l$ at baseline to $229.5\times10^3/\mu l$ at follow-up; the decrease was evident by 1 month. In no case, however, did platelet counts fall below the normal range.

None of the patients had evidence of preexisting liver disease when the valproate regimen was initiated. Most of these individuals received treatment for bipolar disorder and substance use, and many decreased their substance use significantly during the review period. However, in a subgroup of eight individuals identified through patient progress notes who continued to drink during valproate therapy, there were also no significant elevations in their level of liver transaminases. Individuals with alcoholism in the current project exhibited elevated γ-glutamyltransferase levels, suggesting that they may have had some degree of alcoholic fatty liver disease. Despite this effect, individuals did not continue to develop higher elevations of liver transaminase levels. In fact, the level of liver transaminases tended to decrease over time.

From these data, it appears that moderate doses of valproate (with an average blood level of approximately 70 mg/liter) in alcoholics without significant impairment of liver function do not cause significant adverse effects on WBC count, platelet count, or liver transaminase level.

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Ketanserin Treatment of Tourette's Syndrome in Children

TO THE EDITOR: Gilles de la Tourette's syndrome is a complex neurological disorder characterized by multiple motor and vocal tics, associated behavioral disturbances, and a chronic fluctuating course. Treatment of Tourette's syndrome is often unsatisfactory, even with drugs such as haloperidol, pimozide, or clonidine, some of which carry the risk of serious adverse effects (1). Recently, risperidone, which combines highly potent serotonin 5-HT_2 and potent dopamine antagonist properties, has been described to decrease motor and vocal tics in Tourette's syndrome without major side effects (2, 3). Ketanserin is also a strong 5-HT_2 antagonist and an α_1-adrenergic agonist, but this drug's activity with the dopamine receptor is 200 times weaker than that of haloperidol or risperidone (4, 5).

We investigated ketanserin treatment with seven children (four girls and three boys, 9 to 16 years of age) with Tourette's syndrome conforming to DSM-III-R criteria. The children's parents were fully orally informed about ketanserin and its potential side effects. Four children had received previous classical medications—haloperidol, pimozide, and clonidine principally—without improvement in two children, with relapse after 1 year in one child, and with relapse after 2 years in the fourth. Three other children received ketanserin as their first medication. Ketanserin was given in an initial dose of 20 mg/day. Six children showed a dramatic improvement within a few days. Total disappearance of tics was obtained with doses up to 240 mg/day (mean=120 mg/day). One boy withdrew from the study because of lack of response after 2

months. Ketanserin was stopped in one child after 4 months because of orthostatic hypotension. In two cases, tics reappeared after 4 and 7 months despite higher doses. As for the three other children, one was lost to follow-up after 6 months, and two were still free of tics more than 1 year later.

To our knowledge, this is the first report of a clinical trial with ketanserin, a serotonergic antagonist, in children with Tourette's syndrome. Our results confirm the important role of the serotonergic system in the pathogenesis of Tourette's syndrome, although hypotension likely relates to its blockade of α_1-adrenergic receptors; this may also play a role in the control of tics. On the basis of these trials, further controlled studies with selective 5-HT_2 antagonists will be considered, especially in children.

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Hallucinogens and Obsessive-Compulsive Disorder

TO THE EDITOR: Several recent studies have documented an association of a serotonin 5-HT_{2A} receptor promoter polymorphism, -1438G/A, with anorexia nervosa (1). Now the same genetic association has been extended to obsessive-compulsive disorder (OCD) (2), the symptoms of which have been shown to share considerable commonality with anorexia (3). Since such functional promoter variants usually alter transcription frequency and thereby affect receptor population, drugs that selectively induce down-regulation of 5-HT_{2A} receptors might alleviate the symptoms of anorexia and OCD.

It is known that the classic psychedelic drugs—LSD, psilocybin (the active agent in *Psilocybe* mushrooms), and mescaline (the alkaloid in peyote cacti)—act as agonists at 5-HT_{2A} receptors, inducing a rapid and robust tolerance and cross-tolerance to their hallucinogenic effects by means of down-regulation of the 5-HT_{2A} receptor system (4).

Anecdotal evidence indicates that the symptoms of OCD are mitigated by hallucinogens, and the newly recognized 5-HT_{2A} receptor promoter polymorphism provides the likely mechanism for this effect. Three reports have surfaced in the literature of individuals with long-standing OCD who experienced significant alleviation of their disorder after what was initially a "recreational" use of LSD, peyote, or *Psilocybe* mushrooms. The most recent of these (5) relates that a 34-year-old man who had suffered from OCD since the age of 6 found that both peyote and *Psilocybe* mushrooms moderated his symptoms (which included incapacitating and compulsive counting, showering, and ritualistic washing of his clothes, hands, and body). He began a 4-year course of daily *Psilocybe* mushroom ingestion, which resulted in improvement of his OCD symptoms, unaccompanied by any hallucinogenic effects because of his acquired tolerance. During a subsequent 2-year period, his OCD remained in control without the need for him to ingest *Psilocybe*, but then the symptoms gradually returned to their initial levels.

Some beginnings have been made in studying the effects of psychedelic drugs for alleviating OCD. The potential benefits of these drugs in anorexia nervosa, a devastating and not infrequently life-threatening disorder with few or no fully successful treatment options, should likewise be studied.

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Individualized Risperidone Dosing

TO THE EDITOR: The report by Daniel J. Luchins, M.D., and colleagues (1) using computerized pharmacy data provides important confirmation that less rapid titration of risperidone than originally recommended is warranted. The authors also found that patients were more likely to continue taking risperidone if they had a higher maximum dose (5.7 mg/day versus 4.7 mg/day), noting that 5.7 mg/day "is very close to the recommended dose" for this agent. Although the authors do not specifically advocate 5.7 mg/day as the optimum risperidone dose, readers may draw the erroneous conclusion that because patients receiving this dose had higher continuation rates as a group than those taking 4.7 mg/day, the higher dose (5.7 mg/day) is the best risperidone dose for most patients. However, current clinical practice and some recent experimental data argue for highly individualized dosing of risperidone, as well as lower doses (1–5 mg/day) for many patients. Kopala and colleagues (2) found that lower (2–4 mg/day) versus higher (5–8 mg/day) doses of risperidone were associated with superior outcome for all three symptom clusters on the Positive and Negative Syndrome Scale, as well as lower rates of extrapyramidal symptoms. Similarly, Darby and colleagues (3) found risperidone doses ranging from 1 to 6 mg/day useful in their clinical practice (average daily dose in outpatients=3.3 mg) and showed that daily risperidone doses of 4 or 6 mg may produce roughly equivalent blood levels (risperidone plus 9-hydroxyrisperidone) in any two given patients. (These authors also note that the average dose of risperidone in the United States for

all patients is 4.7 mg/day, although this does not establish an optimal average daily dose.) For children, adolescents, and elderly patients, Ayd (4) recommends not only a very gradual titration schedule but a ceiling dose of 4 mg/day for several weeks before a higher dose is prescribed. Opler (5) advocates an individualized approach to risperidone dosing, with some patients doing well on doses as low as 1 mg/day and others requiring 16 mg/day or more. My own experience confirms the need for slow titration, highly individualized (often low) doses, and in some cases, the use of plasma levels as a guide to treatment.

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Dr. Luchins and Colleagues Reply

TO THE EDITOR: We agree with Ronald Pies, M.D., that the optimal daily dose of risperidone must be individualized and hope our finding that 5.7 mg was the average daily dose of risperidone in patients who continued taking medication does not confuse this issue. It is unfortunate that the original finding by Marder and Meibach (1)—that, on average, 6 mg was the more effective daily dose than 2, 10, or 16 mg—has been interpreted to mean that 6 mg is an optimal dose for all.

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Personality Ratings of Depressed Outpatients

TO THE EDITOR: I would like to take issue with the conclusion of the article by R. Michael Bagby, Ph.D., and colleagues (1). The authors conclude that "depressed mood may not influence the self-report of personality traits." Because they did not measure patients before and after improvement from depression, their design was cross-sectional. As such, it is inadequate for making conclusions about personality measures over time at different levels of depression. This would ideally require longitudinal findings or at least measures on two similar populations that differ by state of depression.

They do cite an article that used a sound longitudinal design to address this question (Hirschfeld et al., 1983) but do not report its empirical findings. This well-designed longitudinal study indicated that depression significantly changes self-report personality findings. There are other reports that indicate a higher level of personality trait measurement from both anxiety and depression (2, 3) and that aspects of these changed measures may have clinical significance (4). (It appears that personality pathology measured when personality traits are exaggerated by state effects may still be predictive, of course.)

Dr. Bagby and colleagues report that informants' ratings of personality indicate that the informants think that the patients, when more depressed, have more neuroticism, less extraversion, and other personality changes. Their findings are consistent with the hypothesis of higher levels of measured personality pathology with higher states of depression. This finding is different from their conclusions.

Finally, the authors reported on only one instrument. Their conclusion should be that cross-sectional data on the NEO Personality Inventory indicate good cross-sectional correlation between patients' and informants' ratings. This would be an appropriate conclusion to their interesting report.

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JAMES REICH, M.D., M.P.H.
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Dr. Bagby and Colleagues Reply

TO THE EDITOR: James Reich, M.D., M.P.H., contends that the only way to assess the effects of depressed mood on the self-report of personality traits is to use longitudinal designs. We disagree. Statistical analyses and methodological designs that incorporate multiple methods in the measurement of personality can provide strong inferential evidence in determining the clinically significant effects of depressed mood on personality traits. In this regard, two findings from our study warrant reiteration.

First, depressed patients' self-reports of personality did not differ from informant ratings even when the informants were specifically instructed to rate these patients as they are usually. Thus, one method of assessment presumed to be influenced by the state effects of depressed mood (self-report) did not differ from a method of assessment (informant ratings) presumed to be not so influenced. The fact that the informants reported being cognizant of the fact that depressed mood does affect in some way a patient's personality suggests that they were able to set aside these potential effects when specifically instructed to do so. Dr. Reich suggests that this very recognition is verification of the effects of depressed

mood on personality. Dr. Reich fails, however, to appreciate the distinction between the influence of depressed mood on personality traits and the accurate assessment of premorbid traits, despite the presence of depressed mood. Most valid measures of personality traits—for example, the NEO Personality Inventory—consist of items that are intended to elicit traits, not states. The data from our study suggest that these questions measure mostly traits (see also reference 1).

The second point to reiterate is that while there were some marginal differences between the self-report ratings and the informant ratings, as determined by standard statistical tests of significance (i.e., t tests), the magnitude of these differences, as determined by the effect size (i.e., Cohen's d), was not clinically meaningful. Dr. Reich did not address this issue in his reinterpretation of the results from our report. This point is best exemplified from the results of an earlier study conducted by our group (2), which examined the differences between acutely ill and fully recovered depressed patients. Although the acutely depressed patients had significantly higher neuroticism and significantly lower extraversion scores than the recovered patients, scores for both patient groups remained in the clinically significant range. Thus, the clinical interpretation for the test scores of the recovered and nonrecovered patients would not change. Finally, it is instructive to note that of the four studies cited by Dr. Reich in support of the position that depressed or anxious mood influences personality traits, not one of them calculated effect sizes or otherwise ascertained the clinical significance of statistical differences.

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Neuroleptic Discontinuation and Tardive Dyskinesia Risk

TO THE EDITOR: Peter N. van Harten, M.D., Ph.D., and colleagues (1) reported that patients whose neuroleptic therapy was interrupted more than twice were approximately three times more likely to develop tardive dyskinesia than those whose therapy was interrupted two times or fewer. This odds ratio was calculated for the lifetime intake of neuroleptics and anticholinergics, and both were not statistically significant. They conclude that neuroleptic therapy should not be interrupted to minimize the risk of tardive dyskinesia. We take exception to such a broad conclusion.

The authors make a rather common error of interpreting correlation as causation. It would seem likely that patients who experienced higher rates of extrapyramidal symptoms through the course of their neuroleptic treatment would be more likely to discontinue medications and thus have more frequent drug interruptions. Since extrapyramidal symptoms predict future development of tardive dyskinesia (2–5), the observed higher risk of tardive dyskinesia associated with antipsychotic drug interruptions is likely driven by the former association (i.e., between extrapyramidal symptoms and tardive dyskinesia). The linear regression model included lifetime anticholinergic use as a predictor variable and found no statistically significant contribution to the model ($p=0.06$). Although one may use the cumulative anticholinergic dose as a proxy of past extrapyramidal symptoms in the analysis, we believe that this does not adequately address the issue raised. This is because antipsychotic drug interruptions may have substituted for anticholinergic drug treatment. Considering this, the authors may want to enter the cumulative anticholinergic dose first in a stepwise regression model to account for the variance explained by extrapyramidal symptoms and subsequent anticholinergic drug treatment before examining the predictive value of drug interruptions. Albeit, this is informative to the extent that the cumulative anticholinergic dose reflects past extrapyramidal symptoms.

Furthermore, we note that total neuroleptic exposure (in chlorpromazine equivalents) has not always been a good predictor of tardive dyskinesia. This is likely because of the broad pharmacokinetic variability found among patients. A more common useful measure has been total time of neuroleptic exposure (6). This variable was not addressed by the article.

In conclusion, the interpretation of a correlation as causation is misleading. We maintain that strategies to treat tardive dyskinesia should include cessation of antipsychotic drug treatment if otherwise clinically feasible.

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Dr. van Harten and Colleagues Reply

TO THE EDITOR: Jay D. Sherr, Pharm.D., and colleagues state that every strategy for treating tardive dyskinesia should include the cessation of antipsychotic drugs if clinically feasible. We strongly support this idea, and it would be a misconception if the opposite was concluded from our article. The central point of our report was that if treatment with neuroleptics is required, the drugs should preferably not be administered intermittently because this may increase the risk of tardive dyskinesia. The authors suggest that we interpreted correlation as causation and that causation may be reversed in such a way that extrapyramidal syndromes are the

cause of drug interruptions. However, it is very unlikely that tardive dyskinesia was the main reason for drug interruptions. Had it been, then one would expect this information to have been noted in the records. Furthermore, our finding is also supported by the results of animal studies (1). We cannot rule out the possibility that acute extrapyramidal syndromes like parkinsonism, akathisia, and acute dystonia were a main reason for drug interruptions; we did not assess the history of acute extrapyramidal syndromes. Because acute extrapyramidal syndromes may be a risk factor for tardive dyskinesia, this idea deserves attention (1). However, it is not likely that in our study this explanation would be valid: according to the patient records, the main reason for those interruptions was discharge from the psychiatric hospital.

Dr. Sherr and colleagues further suggest that 1) the cumulative anticholinergic dose must be entered in the logistic regression analysis before examining the predictive value of drug interruptions and that 2) the total time of neuroleptic exposure should be used instead of the cumulative amount of neuroleptic exposure. Reanalyzing the data on the basis of these two suggestions did not change the results.

The fact that we were unable to find a relationship between the cumulative amount of neuroleptics and tardive dyskinesia in our cross-sectional study may be because of the long mean duration of neuroleptic treatment in our population. A high mean cumulative neuroleptic dose will obscure this relationship (ceiling effect), particularly if the relationship can only be found during the first years of antipsychotic treatment. Incidence studies clearly show that such a relationship does exist (1, 2).

In short, our conclusion that drug interruptions may be a risk factor for tardive dyskinesia seems the most likely explanation from the data.

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Risperidone and Clozapine for Treatment-Resistant Schizophrenia

TO THE EDITOR: G. Bondolfi, M.D., and colleagues (1) recently reported that risperidone was as effective as clozapine in reducing psychopathology in neuroleptic-resistant schizophrenia on the basis of an 8-week, double-blind, multicenter trial conducted in Europe with 86 chronically ill patients with schizophrenia. Other open studies have also suggested the effectiveness of risperidone for some patients with schizophrenia whose positive symptoms did not respond to typical neuroleptics (2–5). Risperidone and clozapine have also been reported to be equally effective with regard to the reduction of psychopathology in neuroleptic-responsive patients with schizophrenia (6).

It is important to carefully examine studies of the relative ability of these two drugs in these two groups of patients with schizophrenia, since definitions and degrees of neuroleptic resistance may vary widely (7) and the psychotic symptoms of neuroleptic-intolerant patients may be equally responsive to the antipsychotic effects of the antipsychotic agents under study, while they may differ markedly in their effectiveness for neuroleptic-resistant patients. Thus, the fact that Dr. Bondolfi et al. (1) included both neuroleptic-resistant and neuroleptic-intolerant patients in their study is a potential confound. Data on the response of neuroleptic-resistant patients should have been reported separately but were not. Even had they been, the overall group size was small and probably lacked sufficient power to find a difference between the two drugs for either or both subgroups. Second, the determination of neuroleptic resistance included in this study was made retrospectively and included trials of only 4 weeks' duration—too brief a period. A third concern is the rapid titration schedule for clozapine and the low final dose (300 mg/day) achieved, both of which should decrease its efficacy. The method of use and dose of risperidone (2–6 mg/day) may have been optimal. The low dose of risperidone no doubt contributed to the finding that motor side effects were less with risperidone than with clozapine. Fourth, the duration of the study may have been too short to find a difference between the two drugs. Clozapine has been shown to require up to 6 months to achieve its full benefits (8, 9). And finally, it is important to note the difficulty of maintaining a blind study with clozapine and risperidone because of their differences in side effects.

It can be safely concluded from this study that a significant proportion of the patients, some of whom may have been neuroleptic-resistant, did respond well to risperidone and had very few side effects. It would be important to know specifically how many of the patients were neuroleptic-resistant. A larger 6-month study of only neuroleptic-resistant patients with schizophrenia—shown to be so with a final run-in trial with typical neuroleptic drugs, a slower titration of clozapine, and multiple, fixed doses of risperidone or clozapine—is needed to confirm that risperidone is as effective as clozapine in treating neuroleptic-resistant patients.

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HERBERT Y. MELTZER, M.D.
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TO THE EDITOR: I am writing regarding the article by G. Bondolfi, M.D., and colleagues comparing risperidone and clozapine in treatment-resistant schizophrenia. The authors state that their results should be interpreted with caution because of the limited number of patients in the study.

This study reports on a conglomeration of treatment-resistant and treatment-intolerant patients without distinguishing between the two groups. Therefore, this population is likely quite different from the densely refractory population used to prove clozapine's efficacy. Some of these patients may not have received the standard low-potency antipsychotics to which they may respond. The lack of rigor with which patients were selected is borne out by the high response rates of over 60% of both groups in this study in the relatively short span of 8 weeks. Previous studies of truly refractory patients have not shown such robust responses. A landmark study by Kane et al. (1) revealed a 30% response rate at 6 weeks in prospectively identified refractory patients treated with clozapine.

My concern is that this study could be used to support the use of risperidone in refractory (as opposed to intolerant) patients, resulting in the delayed use of clozapine. Of greater concern could be its use as a justification to switch patients from clozapine to risperidone, which could lead to serious exacerbations of illness. It is clear that risperidone is an effective antipsychotic that is better tolerated by patients who experience extrapyramidal symptoms while taking standard agents. At present, there is no convincing evidence of its efficacy in treatment-refractory patients. Clozapine remains unique in this regard.

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TO THE EDITOR: We read with interest the recent report by G. Bondolfi, M.D., and colleagues in which the efficacy of risperidone and clozapine in the treatment of schizophrenia was compared in a randomized, double-blind study. However, we have concerns regarding the methodology of this study. In the first place, the size of the treatment-refractory group is unclear. Two 4-week trials with unspecified antipsychotic doses are inadequate for the selection of treatment-refractory subjects, and the retrospective nature of this assessment further limits its usefulness. Indeed, the landmark study by Kane and colleagues that established clozapine's superiority in the treatment of refractory schizophrenia deems patients treatment refractory only after 6 weeks of prospective treatment with adequate antipsychotic doses and only after three previous unsuccessful antipsychotic trials. The difficulty in effectively selecting a substantial number of treatment-refractory patients is borne out in the report's results: 65% to 67% response rates after 8 weeks of treatment are consistent with treatment response in an unselected, rather than a treatment-refractory, group. In the Kane et al. study, only 30% of the patients responded after 6 weeks. Second, clozapine dosing appears to have been rather conservative, given that mean concentrations in the nonresponder group were 292 ng/ml. There is evidence that treatment-refractory patients may need concentrations over 350 ng/ml (1) in order to derive benefit from clozapine treatment. Thus, more patients may have responded to clozapine had they been given higher doses. Third, it has been suggested that response to clozapine may be delayed 6 months or longer after a therapeutic dose is achieved (2). Therefore, a longer observation period may have yielded further responses to clozapine treatment of potential significance for this study, especially had the dose been titrated upward in unimproved patients.

We agree with the authors that long-term, comparative trials between risperidone and clozapine, as well as olanzapine and quetiapine, in more homogeneous patient groups are needed. We also think that the previously mentioned limitations to their study preclude extending their conclusions to treatment-refractory schizophrenic patients. Definitive trials are needed to establish risperidone's efficacy with treatment-refractory schizophrenia.

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Drs. Bondolfi and Baumann Reply

TO THE EDITOR: Herbert Y. Meltzer, M.D., Eugene Rubin, M.D., Eduardo Dunayevich, M.D., and Anjan Chatterjee, M.D., raise three main concerns about our report: 1) study group population; 2) clozapine titration, dosing, and delayed response; and 3) risperidone with treatment-resistant patients and switching from clozapine to risperidone.

1. Our patient group was typical for the standards used when treatment with clozapine is envisaged—i.e., intolerance or nonresponse to previous treatments (see Method). Therefore, our group cannot be compared with that of the Kane et al. study, in which treatment refractoriness was defined more rigorously, both retrospectively and prospectively, and in which nontolerant patients were not included. As outlined in our Discussion section, treatment resistance and treatment intolerance could not be clearly differentiated, and this could indeed be one of the reasons for the higher response rate we found.

As a consequence of the Kane et al. study, the definition of treatment resistance—two rather than three retrospective trial failures with conventional antipsychotics for a 4-to-6-week period, rather than a strict 6-week period—are now accepted (1). Furthermore, now that antipsychotics that are potentially effective and less toxic compared to clozapine are

available (2), a less restrictive definition of treatment resistance may be needed; a multiaxial classification of treatment resistance that focuses on specific targets, such as positive and negative symptoms, treatment intolerance, and poor compliance, may be helpful in directing treatment.

2. Questions concerning clozapine doses, plasma levels, and delayed responses were addressed in our report. We emphasized "cultural" differences in clozapine dosing between Europe and the United States, we reported that plasma concentrations of clozapine of less than 350 ng/ml are reportedly sufficient, and we insisted that doses as high as 600 mg/day and 12 mg/day of clozapine and risperidone, respectively, can be given. An adaptation of the clozapine dose on the basis of plasma concentrations was prohibited because the code would have been broken. About the relative rapid titration schedule for clozapine, as outlined in our Discussion section, the differences in side effects observed during the titration period suggest that some bias may have occurred with regard to the blindness of the trial.

3. We think that patients who do well taking clozapine and are able to tolerate its side effects should continue taking it. Otherwise, it seems reasonable to consider a trial of risperidone with treatment-resistant schizophrenic patients before using clozapine. About 30% of such patients show no significant change in either positive or negative symptoms when treated with clozapine (3). Moreover, risperidone efficacy in subpopulations of patients with variously defined treatment resistance may corroborate the hypothesis of heterogeneous physiopathology of resistant schizophrenia, which may be discriminated by pharmacological response to agents with different pharmacodynamic profiles (4).

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Fetal Alcohol Exposure and Adult Psychiatric Disorders

TO THE EDITOR: Chris Famy, B.S., and colleagues (1) reported on mental illness in adults with fetal alcohol syndrome or fetal alcohol effects. This report seems timely because there is little study of adult psychiatric sequelae of such neurodevelopmental disorders, although such sequelae may be common, as suggested by this study.

Yet, this was a preliminary study because it was descriptive rather than controlled. Furthermore, the final group size was small and most probably biased by selection, because the more severely ill subjects were excluded—i.e., the 9% that were (at least mildly) mentally retarded. Even if this was meant to control for the usual psychiatric comorbidity of any mental retardation, no explanation was provided for the relatively small percentage of individuals with arrested mental development, which is reported to be about 50% or more in persons with fetal alcohol syndrome and fetal alcohol effects (2). In addition, the severity of psychiatric symptoms was not established (by standard means such as self-report and clinician-rated questionnaires). Further studies should address these issues and control for environmental confounders by comparing subjects with fetal alcohol exposure who developed in different environments, as well as subjects with and without fetal alcohol exposure who developed in similar environments. Different alcohol- and non-alcohol-related neurodevelopmental disorders should also be compared. The long-range (adult) psychiatric impact on the fetus of moderate and binge drinking during pregnancy—which do not result in fetal alcohol syndrome or fetal alcohol effects—should be studied, considering that such maternal alcohol drinking has been empirically associated with learning problems and with the lowering of IQs in children exposed to alcohol in this way during fetal development (3).

An interesting finding of this report is that schizophrenia, in contrast with other psychotic disorders, was not observed in the adults with clinically significant fetal alcohol exposure. This finding may be incidental or because of the small group studied. A more interesting explanation may be that the neuropathology caused by fetal alcohol exposure is different from the neuropathology of schizophrenia. This is compatible with evidence from animal and human studies of diffuse—but especially limbic system and midline—brain damage in utero because of alcohol use (4–6), whereas negative syndrome (nonpsychotic) schizophrenia manifests especially as frontal lobe dysfunction (7). Such comparisons provide important information linking different clinical disorders to distinct neuropathological lesions and should be extensively studied for psychiatric and neurodevelopmental disorders in order for both to be better understood and treated.

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Dr. Famy and Colleagues Reply

TO THE EDITOR: We were pleased to hear that our recent article stimulated interest in the mental illness manifested by adults with fetal alcohol syndrome and fetal alcohol effects.

As Abraham Rudnick, M.D., Dipl.Psych., and Asher Ornoy, M.D., point out, this was a first small pilot study.

The deletion of subjects with IQs of 70 or less was because of the administrative requirements of the Structured Clinical Interview. The fact that this restriction omitted only 9% of otherwise eligible subjects may be partly a manifestation of the difficulties of locating disabled people after they leave home and school. Comparison with IQ data from a Finnish study of 2-year-old children (Autti-Ramo et al., 1992) would be difficult because of marked differences in the age of the subjects, assessment tools, environment, and culture.

We agree with Drs. Rudnick and Ornoy that the severity of psychiatric symptoms should also be studied; such a study is already under way on our unit, involving subjects participating in a study of neuroanatomic and neuropsychologic deficits of fetal alcohol syndrome and fetal alcohol effects.

We also agree that dose/response issues and environmental factors are important considerations in studying the long-term impact of teratogens such as alcohol. These are best studied in longitudinal prospective designs where the dose is established prenatally, the environment documented prospectively, and the outcomes assessed developmentally. Recent prospective research reveals continuing effects of prenatal alcohol exposure on psychosocial and cognitive functioning (1) and alcohol problems (2) in 14-year-old offspring. Studies such as these can also address prevalence issues that are otherwise difficult to study in patient groups. The overall prevalence of fetal alcohol syndrome (e.g., diagnosed blind at birth) and alcohol-related neurodevelopmental disorders (as described by the U.S. Institute of Medicine [3] and assessed throughout the first 7 years of life) was at least 9.1 in 1,000 in a recent study (4).

The hypothesis suggested by Drs. Rudnick and Ornoy—that people with schizophrenia and fetal alcohol syndrome or fetal alcohol effects may have different structural anomalies of the brain—may be correct, but this work is only in its first stages. Recent magnetic resonance imaging studies show hypoplasia of the corpus callosum with both conditions, but the geometry of the callosal alcohol effect is different and less sharply localized than the group difference with schizophrenia (5; unpublished study by F.L. Bookstein et al., 1998). It is premature to draw conclusions about the differential neuropathology of schizophrenia and fetal alcohol syndrome. We agree with Drs. Rudnick and Ornoy that much more research is needed and hope that these brief interchanges will stimulate additional work at other centers.

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CHRIS FAMY, B.S.
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Treatment of Panic Disorder

TO THE EDITOR: Andreas Broocks, M.D., and colleagues (1) say that in their controlled trial, the therapists avoided exposure techniques. However, aerobic exercise (running) itself is a method to induce prolonged exposure to feared agoraphobic situations along the 4-mile route (park or forest) near home. Asking patients to complete the route at least three times a week and to present activity diaries weekly to the therapists can be seen as further exposure/homework instruction. Moreover, as the authors note, running exposes patients to the internal feared cues of palpitations, sweating, rapid breathing, and the like that are induced by exercise. The two patients who panicked while running continued to run and improved within 15 minutes, as usually happens during exposure therapy. Exercise per se, however, may not induce exposure to all of the cues that panic disorder sufferers fear in the manner required for optimum outcome. The study may have achieved even more improvement had its exposure been tailored to involve all of the patients' feared cues systematically rather than just incidental to the exercise schedule.

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Drs. Broocks and Bandelow Reply

TO THE EDITOR: We thank Isaac Marks, M.D., F.R.C.Psych., for his interesting comment. He pointed out that exercise itself induces prolonged exposure to some situations that are often avoided by patients suffering from panic disorder with agoraphobia. Although we tried to avoid specific cognitive or exposure techniques, we agree that is impossible to perform outdoor running without having exposure at the same time. Some of our patients had marked initial difficulties in coming to our running group once a week and could only run when a friend or relative accompanied them. In such cases, our study design did not allow for encouraging the patients to run on their own in order to increase the intensity of exposure. Yet, we are not able to separate the therapeutic effects of motor activity from the beneficial effects of exposure. To do so, it would be necessary to have one group of patients exercising at home (e.g., by using bicycle ergometry) and to compare this group to patients treated by standard exposure techniques and—if possible—to a third group with combined exercise and exposure treatment. However, mere motor activity at home would confront patients with internal stimuli such as sweating and palpitations that might lead to interoceptive conditioning. Dr. Marks emphasizes that such a mechanism might also contribute to the beneficial effects of

exercise. We mentioned in our Discussion that interoceptive conditioning has indeed been used in cognitive behavioral approaches to help patients reattribute certain somatic cues to nonpathological vegetative functions. Again, for methodological reasons, we did not discuss these experiences and cognitions with the patients from our study, in an attempt to restrict the brief talking sessions to general support only. However, we observed that the experience of being able to run 3 or 4 miles does not remain without influence on dysfunctional cognitions, especially those related to somatic concerns. A more detailed analysis of Dr. Bandelow's Panic and Agoraphobia Scale subscales revealed that the most prominent effect of exercise was related to a marked decrease of somatic concerns (59.5% mean change from baseline).

In conclusion, we fully agree with Dr. Marks's expectation that the therapeutic effect of exercise could be further improved by integrating exercise into an individually tailored exposure therapy and—we think—other cognitive-behavioral approaches.

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Lithium Discontinuation

TO THE EDITOR: The study by William Coryell, M.D., and colleagues (1) about lithium discontinuation-induced refractoriness, although informative, has two major drawbacks.

First, a study group consisting of 28 patients is inadequate to detect a phenomenon that, although clinically significant and potentially fatal (2), is certainly not frequent. It is useful to mention, is this connection, that although Tondo et al. were unable to find an effect of lithium discontinuation in their study group of 86 patients—to which Dr. Coryell et al. refer in their article—they actually detected this effect in a group of 106 patients (3), in which they found that "the proportion of time ill rose significantly (by 38%)" during the retreatment period.

Second, Dr. Coryell and colleagues provide no information on the treatment received by their patients before entering the study. As far as we know, these patients may already have interrupted their lithium treatment before the index episode, which, of course, would introduce a bias.

We should not forget that the patients described by Post et al. (2) had been receiving successful, continuous lithium prophylaxis for as long as 6 to 15 years before discontinuation and had experienced many relapses during a short period following lithium reinstitution. We should look carefully at the impressive life charts and case reports provided by these authors and by other experienced clinicians such as Goodwin (cited in reference 2) and Koukopoulos et al. (4) before dismissing a clinically meaningful phenomenon on the basis of studies that are carefully conducted but probably do not have adequate statistical power.

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Dr. Coryell and Colleagues Reply

TO THE EDITOR: Mario Maj, M.D., Ph.D., raises two caveats regarding our report—that the statistical power was small and that bias may have resulted from the inclusion of some patients who had discontinued lithium previous to study entry.

To illustrate the first concern, Dr. Maj noted that the Tondo et al. group elsewhere described an extended study group in which patients experienced a significantly higher proportion of time ill during the retreatment period. Because this study group was mentioned as "unpublished data" in a review chapter published in the same year as the Tondo et al. article, the methods used to acquire and describe the additional subjects are difficult to critique. Dr. Maj's point, though, does raise a methodological issue to which our report only alluded.

Study groups drawn from treatment-seeking populations are biased toward relative illness severity and persistence. By the same token, patients who are attending a clinic more frequently are more likely to be in a problematic phase of their illness than those with less frequent visits. If the group described by Tondo et al. was drawn from all of those "attending" a clinic in a given period of time, those who were experiencing a relatively difficult period in their illness would be overrepresented, and this would produce the impression that current therapies are less effective than past therapies. The prospective ascertainment of illness course provided with our data avoids this problem in that patients were tracked regardless of whether, or how often, they continued to seek treatment.

The limited statistical power in our data would have been notable had trends existed toward longer times for recovery in the second treatment phase. A trend in the opposite direction was apparent, however; nearly 50% of the patients had recurrences within 2 years in the first well period, but just over 30% had recurrences within that time in the second well period.

It may be, as Dr. Maj's second point implies, that the first lithium discontinuation—although not subsequent discontinuations—increases the likelihood of subsequent therapeutic resistance. We are not aware that this has been asserted in the pertinent literature, however.

We do not wish to prematurely dismiss the possibility that lithium discontinuation has long-term effects on lithium responsiveness. Given the biases likely to be operating in the reports of this effect, though, its application in clinical management would be premature at this point. Other prospectively observed study groups of patients with bipolar disorder exist, and the data from those studies could help settle this question.

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