Letters to the Editor

Clarithromycin-Induced Mania

TO THE EDITOR: This letter presents a case of clarithromycin-induced mania.

Ms. A, a 52-year-old woman with a history of three depressive episodes, was admitted for hyperenergetic, loud, and unfocused behavior. She was also elated and delusional. Two days earlier, she had been prescribed a regimen of clarithromycin, 500 mg b.i.d., and prednisone, 60 mg q.i.d., followed by a taper, for severe sinusitis. Results of a neurologic examination were within normal limits; laboratory data were also within normal range. The results of a drug-of-abuse screen were negative; Ms. A's blood alcohol concentration was zero. Her clarithromycin was discontinued; the prednisone taper continued. Within 1 week, Ms. A responded to haloperidol and lithium treatment. She was tentatively diagnosed as having steroid-induced psychosis. Lithium was discontinued after 4 months because of the appearance of hypothyroidism, probably induced by lithium. Two years later, again 2 days after starting treatment with clarithromycin for an acute episode of sinusitis, Ms. A became agitated and acutely delusional. She believed she was "Jesus Christ," a singer and a superstar. She would scream intermittently. She had an expansive mood, flight of ideas, an intense affect, and looseness of associations, but no hallucinations. Her physical examination and laboratory results were unremarkable. Clarithromycin was discontinued, and Ms. A was started on a regimen of haloperidol and lithium. An unequivocal improvement was noted the next day with mildly pressured speech and an expansive mood, but a denial of delusions. Ms. A was discharged 6 days after her admission.

Ms. A had two similar episodes with clear evidence of mania and psychosis. During the first episode, she was taking both clarithromycin and prednisone; the mania and psychosis were thought to be due to the prednisone. Before the second episode, Ms. A was taking clarithromycin alone. We think that Ms. A's case represents clarithromycin-induced mania. Her dose of clarithromycin in both episodes was 500 mg b.i.d. as opposed to the relatively high doses (1000 mg b.i.d.) described in the treatment of disseminated *Mycobacterium* avium-complex infections in two AIDS patients who developed manic episodes (1), similar to the results reported by Cone et al. (2). Clarithromycin has excellent CSF penetration (3), but no reports of possible interaction with central neurotransmitters were found in the literature, although such interaction is a plausible assumption. There have been several reports of CNS side effects of clarithromycin: dizziness, lightheadedness, confusion, and insomnia (4), as well as visual hallucinations (5).

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Violent Behavior Associated With Donepezil

TO THE EDITOR: We report a case of violent behavior following the commencement of donepezil, the first recently introduced reversible cholinesterase inhibitor in this country. The indication for donepezil is symptomatic treatment of mild or moderate dementia in Alzheimer's disease. Donepezil is thought to work by increasing the availability of intrasynaptic acetylcholine in the brains of patients with Alzheimer's disease (1).

Mr. A, a 76-year-old man with a 2-year history of cognitive impairment, was clinically diagnosed as suffering from Alzheimer's disease according to ICD-10 (2). His Mini-Mental State score (3) was 17 of 30. There was no history of violence or behavioral disturbances, and no psychotic phenomena were elicited. Apart from an unstable bladder requiring prescription of oxybutinin, 3 mg t.i.d. for the past 5 years, Mr. A's medical history was unremarkable. A physical examination and routine laboratory investigations showed no abnormalities, apart from an intermittent parkinsonian tremor of his left hand. This raised the possibility of a diagnosis of dementia with Lewy bodies (4), although no other features were present. Mr. A was started on a regimen of donepezil, 5.0 mg daily.

Five days later, Mr. A became very paranoid, believing that his wife had been stealing his money. He beat his wife and held her hostage in their house with a knife until their daughter intervened. Mr. A agreed to hospital admission, avoiding compulsory detention.

Physical and laboratory investigations were repeated, including a computerized tomography scan of the brain showing no abnormalities apart from generalized atrophy. Mr. A was started on a regimen of haloperidol, 0.5 mg b.i.d., while his donepezil and oxybutinin were discontinued. His paranoid ideation resolved within a few days and did not reoccur, despite withdrawal of haloperidol.

Although a causal relationship between this violent incident and donepezil cannot be proven, a temporal relation-

ship between the commencement of donepezil and the occurrence of behavioral disturbance in Mr. A, a patient with no previous history of violence, warrants caution with the prescription of this drug. The manufacturer reports that 5% of patients taking donepezil have developed agitation, although only 1% with physical aggression (personal communication). We suggest the need for close specialist monitoring of this recently licensed drug.

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Use of Herbal Products and Symptoms of Bipolar Disorder

TO THE EDITOR: There is an increasing interest by consumers in the use of herbal preparations as an alternative form of treatment for various health problems. This may be due, in part, to the increasing cost of modern health care, to consumers' turning to a more natural lifestyle, or to an increased interest in health and improved quality of life. A telephone survey of 1,539 adults (1) revealed that 34% had used some form of unconventional therapy (including acupuncture, hypnotherapy, homeopathy, macrobiotics, and 12 other modalities) within the past year; of that group, 3% had used herbal remedies. We present a case in which the effects of concomitant use of herbal products mimicked a psychiatric condition.

Ms. A, a 40-year-old white married woman diagnosed with bulimia without purging, was referred for consultation and follow-up. She described episodes of depressed mood, crying spells, anger, irritability, and bloating that began before her menstruation and resolved with the onset of her period. She also described episodes of manic-like symptoms lasting up to a week that had begun in the past year: she felt full of energy and irritable and experienced decreased need to sleep and trouble concentrating. Ms. A was not taking any prescription medication other than levothyroxine for hypothyroidism.

A provisional diagnosis of premenstrual dysphoric disorder and mood disorder not otherwise specified was made in addition to bulimia nervosa. Fluoxetine was prescribed for Ms. A's current depressed mood and bulimia. She was monitored for any manic-like symptoms. About 5 months later, Ms. A admitted that she had recently discontinued her regimen of fluoxetine. Her depressed mood had resolved, but her episodes of bingeing continued. Ms. A explained that it was important to lose weight so that people would notice her. Exercising up to 3 hours per day to lose weight was not enough. Ms. A now admitted that, for over a year, she had been periodically treating herself with herbal products from the health food store to augment her weight loss. These products contained ma-huang (ephedra), chromium picolinate, and caffeine. Further questioning revealed that when Ms. A took these products, she felt an increase in energy and a decrease in appetite. She would sleep 2–3 hours at night and be irritable the next day. Ms. A continued taking this combination for about 5–10 days until she reached a predetermined weight or was not able to function. When she stopped taking the herbal products, Ms. A experienced hypersomnia, dysphoria, poor concentration, and fatigue. She would return to the herbal regimen when she felt the urge to lose weight.

In this case, the effects of self-medication with herbal products mimicked the symptoms of mania. A misdiagnosis may needlessly expose the patient to unwarranted medications. Patients should be specifically questioned about the use of herbal products during routine visits. The clinician's awareness of any herbal products the patient is taking may improve the quality of treatment and prevent potential complications.

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Antidepressants in Depressed Patients With Irritable Bowel Syndrome

TO THE EDITOR: Irritable bowel syndrome is a common gastrointestinal disorder accounting for 50% of cases seen by gastroenterologists (1). Irritable bowel syndrome is frequently associated with major depressive disorder, which has been diagnosed in approximately 15% of active cases (2). Thus, it is common that patients with irritable bowel syndrome may be treated with psychotropic medications.

Although the use of tricyclic antidepressants has been described in the treatment of irritable bowel syndrome (2), we failed to find any literature on the use of selective serotonin reuptake inhibitors (SSRIs) in these patients. Since SSRIs are the most widely used antidepressants, it is important to know if they are well tolerated by patients with irritable bowel syndrome. This is of particular concern since SSRIs are associated with 10 times higher prevalence of gastrointestinal side effects than are tricyclic antidepressants (3). We present a case study that deals with this issue.

Ms. A, a 42-year-old Caucasian woman with a 20-year history of irritable bowel syndrome that had been in remission for the last 2 years, sought psychiatric treatment for the symptoms of major depressive disorder (depressed mood, low energy, decreased sleep, poor appetite, and feel-

ings of guilt). She began a course of sertraline, 50 mg q.i.d.; a remission occurred within 3 weeks. During the eighth week, Ms. A developed profuse diarrhea, feelings of abdominal distention, and weakness—consistent with her symptoms during the prior exacerbation of irritable bowel syndrome. After 2 days of suffering from abdominal symptoms, she stopped taking her sertraline; by the next day, she was free of the symptoms of irritable bowel syndrome. Unfortunately, her depressive symptoms recurred within a week. Because of the clinician's belief that sertraline may have been implicated in Ms. A's irritable bowel syndrome exacerbation, Ms. A began taking bupropion, a medication that predominantly blocks norepinephrine and dopamine reuptake. She was started on a regimen (100 mg b.i.d.) of the sustained-release preparation and responded within 3 weeks with full remission of her depression. Irritable bowel syndrome had not recurred after 4 months of treatment.

The case study suggests that SSRIs may exacerbate the symptoms of irritable bowel syndrome. This exacerbation is consistent with the well-known gastrointestinal side effects of SSRIs, which appear to be related to the effect of serotonin on 5-HT_3 receptors in the gut (4). Although SSRIs have many advantages over earlier antidepressants, the treatment of choice for patients with irritable bowel syndrome and major depressive disorder may be tricyclic antidepressants, as well as other nonserotoninergic agents (e.g., bupropion).

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Response of the Parkinsonian Symptoms of Multiple System Atrophy to ECT

TO THE EDITOR: Multiple system atrophy is a sporadic degenerative disorder characterized by parkinsonism, dysautonomia, and ataxia in any combination (1). The parkinsonian symptoms of multiple system atrophy are poorly responsive to levodopa therapy (2), unlike Parkinson's disease in which the motoric symptoms respond to dopaminergic agents and ECT. We present a case report of a patient with multiple system atrophy and comorbid major depression whose parkinsonian symptoms responded to ECT.

Mr. A was a 78-year-old man who at the age of 72 had developed bradykinesia, rigidity, resting tremor, ataxia, orthostatic hypotension, and urinary incontinence. His parkinsonian symptoms were poorly responsive to carbidopa and levodopa; Mr. A was unable to transfer (i.e., move from his bed to a chair) or walk independently. At the age of 75, he had developed antidepressant-refractory major depression.

Following outpatient neurology and psychiatric evaluations, Mr. A was referred for inpatient psychiatric treatment. Upon admission, he reported a depressed mood, anhedonia, anergia, frequent nocturnal awakenings, decreased appetite, feelings of guilt, and a fixed belief that "people were plotting" against him. His score on the Mini-Mental State examination) was 27 of 30; on the Hamilton Rating Scale for Depression, his score was 41. Mr. A's diagnosis was major depression with psychotic features; following informed consent, he received eight bilateral ECT treatments (EEG seizure duration=409 seconds) without complication. Carbidopa and levodopa (25 and 100 mg, respectively; two and one-half tablets q.i.d) were continued throughout the ECT course. Following the second treatment, improvement in bradykinesia was noted. After the fifth treatment, Mr. A was reevaluated by the neurology service, and the degree of rigidity, resting tremor, and gait instability was improved. Specifically, Mr. A was able to transfer himself from one position or station to another and walk with minimal assistance. Improvement in his parkinsonian symptoms occurred before the antidepressant effects of ECT were clinically evident. His post-ECT scores on the Mini-Mental State and the Hamilton depression scale were 24 of 30 and 7, respectively. Six bilateral maintenance ECT treatments were administered during the 4 months following discharge. Improvement in parkinsonian symptoms was sustained, and Mr. A was able to transfer himself from one position or station to another and walk independently.

To our knowledge, this represents the first case report where the parkinsonian symptoms of multiple system atrophy responded to treatment with ECT. In a MEDLINE search, one previous case report was identified in which ECT was used to treat combined multiple system atrophy and major depression (3). In this report, the patient 's depression responded to 10 right unilateral (nondominant) ECT treatments (EEG seizure duration=462 seconds), but there was no improvement in his parkinsonian symptoms. It was speculated that bilateral ECT may have been more effective and further postulated that putaminal postsynaptic dopaminergic dysfunction renders the parkinsonian symptoms of multiple system atrophy refractory to treatment with ECT.

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Cocaine and Catatonia

TO THE EDITOR: Here we describe a case of apparent cocaine-induced catatonia. To our knowledge, catatonia related to cocaine use has not been previously reported.

Her mother brought Ms. A, a 36-year-old woman with no prior psychiatric history except cocaine abuse, to the emergency ward after 6 days of bizarre and withdrawn behavior following a crack-cocaine binge. In the emergency ward, Ms. A continued to exhibit mutism, staring, active resistance to being touched or moved, and purposeless, stereotyped hand gestures. Haloperidol (1 mg i.m.), administered for presumed cocaine-induced psychosis, had no effect. A psychiatric consultant diagnosed catatonia and administered lorazepam (2 mg i.m.). Two hours later, Ms. A was alert, oriented, cooperative, and responsive to questions and commands. Her vital signs and results of laboratory tests and physical examination were unremarkable except for cocaine in her urine.

We suspect that cocaine-induced catatonia may be underrecognized in emergency ward settings. For example, Ms. A's medical record revealed two prior admissions for "altered mental status" following cocaine use. During each admission, the patient was withdrawn and mute with a period of bizarre agitation preceding the first episode. In neither case was a diagnosis of catatonia considered.

Recognition of catatonia is clinically important because antipsychotics have been reported to precipitate neuroleptic malignant syndrome in catatonic patients (1). This observation fits with the hypothesis that neuroleptic malignant syndrome is a variant of catatonia (2, 3). Interestingly, cocaine use has shown other connections to the catatonia-neuroleptic malignant syndrome spectrum. A higher incidence of neuroleptic malignant syndrome has been reported among cocaine abusers receiving neuroleptics (5.1%) than among nonusers (4), and the syndrome of hyperthermia, delirium, and rhabdomyolysis following cocaine use overlaps with several key features of neuroleptic malignant syndrome (5). These findings suggest that the increased risk of neuroleptic malignant syndrome among patients with catatonia or cocaine abuse may be related to shared alterations in dopamine systems and provide a possible explanation for the observations in this case report.

The implications of this case are that cocaine-related catatonia may be underrecognized in the emergency ward setting and that antipsychotic treatment of catatonia or cocaine-induced conditions may be associated with an increased risk for developing neuroleptic malignant syndrome. Benzodiazepines and ECT are still the treatments of choice for catatonia of any etiology.

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Sertraline in the Treatment of Clozapine-Induced Obsessive-Compulsive Behavior

TO THE EDITOR: It has been reported that obsessive-compulsive behavior may emerge in patients treated with clozapine (1). This report describes treatment of clozapine-induced obsessive-compulsive behavior with sertraline, which avoids liver enzyme competition.

Mr. A, a 39-year-old white man with a 20-year history of paranoid schizophrenia, was treated with multiple traditional antipsychotic medications. He had begun a regimen of clozapine for treatment-refractory psychosis 8 years previously; he showed significant clinical improvement on a dose of 900 mg/day. After 2 years of treatment with clozapine, Mr. A developed severe obsessive-compulsive behaviors including meticulous checking and hand washing to the point of skin excoriation. For nearly 1 year subsequently, Mr. A refused to take clozapine and was treated with risperidone. During this time, his obsession with germ contamination gradually diminished but did not disappear. He was treated with clomipramine, 75 mg/day, with further reduction of obsessive-compulsive symptoms (2). Unfortunately, on this regimen, compared with his previous treatment with clozapine, Mr. A's psychotic symptoms did not improve. At Mr. A's request, risperidone and clomipramine were discontinued, and clozapine treatment was restarted. His psychotic symptoms improved significantly, but fluvoxamine was substituted to avoid both the return of compulsive behaviors and the potential anticholinergic side effects of clomipramine. Mr. A's obsessive-compulsive behavior did indeed improve with fluvoxamine at a dose of 150 mg/day; however, his clozapine blood level began to rise above 700 ng/ml. His clozapine dose was decreased to 600 mg/day (blood level=2295 ng/ml). Clozapine was further decreased to 325 mg/day (blood level=906 ng/ml) and fluvoxamine to 50 mg/day. Although the clozapine blood level remained high, Mr. A responded poorly to these medication changes by becoming more psychotic and agitated. It appears that the addition of fluvoxamine interfered with the efficacy of clozapine, even though the plasma level was higher. This demonstrates that there was not an absolute correlation among clozapine plasma level, dose, and therapeutic response. Fluvoxamine was discontinued, and sertraline, 100 mg b.i.d., was substituted. Subsequently clozapine was raised to 475 mg/day (blood level=307 ng/ml), and Mr. A's psychotic and obsessive-compulsive symptoms were well controlled.

The case report illustrates the emergence of obsessive-compulsive behavior with the use of clozapine. Marked increase of clozapine blood level occurred when clozapine was combined with fluvoxamine. There was, however, successful management of obsessive-compulsive behavior with sertra-

line without increased blood level of clozapine. The elevated clozapine level with fluvoxamine (3, 4) may be explained on the basis of its competitive inhibition of liver P450 isoenzymes. Clozapine is metabolized through P450 2D6 and IA2 isoenzymes. Fluvoxamine is unique among the selective serotonin reuptake inhibitors in its inhibition of P450 IA2. Thus, fluvoxamine appears to affect the serum level and efficacy of clozapine. Sertraline, on the other hand, proved to be a better choice in the treatment of clozapine-induced obsessive-compulsive behavior because it had no effect on P450 IA2 isoenzyme and moderate effect on 2D6 isoenzyme (5); sertraline did not affect the clozapine serum level or efficacy. Other drugs like paroxetine or fluoxetine, used in the treatment of obsessive-compulsive disorder and not metabolized by P450 IA2, should theoretically also be considered.

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Catatonia Treated With Transcranial Magnetic Stimulation

TO THE EDITOR: In animal studies, transcranial magnetic stimulation is reported to have some properties similar to ECT and to have therapeutic properties in depression. Therefore, we hypothesized that transcranial magnetic stimulation might be effective in treating catatonia. We report a case of catatonia treated with transcranial magnetic stimulation.

Ms. A, a 24-year-old Bedouin woman with a history of an acute psychotic episode 1 year earlier, was admitted in a severe catatonic state. Three days before admission, she had stopped eating, drinking, and speaking. On admission, she was stuporous, automatically obeying simple orders. She had psychotic mutism and negativism with a remarkable waxy flexibility and rigidity. She could not walk. Ms. A was in this state throughout the day, except for brief periods of time. After 15 days' treatment with the maximal dose of haloperidol (3 mg daily) that she could tolerate, a dose that had resolved her previous psychosis, there was no change in Ms. A's catatonic state; in addition, she showed a worrisome weight loss. We considered ECT treatment.

We obtained informed consent from both parents of Ms. A, a compassionate use permit from the Ministry of Health, and written consent from Ms. A during a brief period of cooperativeness in the presence of both her parents.

Repetitive transcranial magnetic stimulation was delivered by a Cadwell High Speed Magnetic Stimulator device with a 90-mm planar coil. Stimulation was given over the right prefrontal cortex. The stimulus was 20 Hz (train duration: 2 seconds; intertrain interval: 58 seconds) 20 times per daily session for 10 working days. The intensity of the stimulus was 80% of patient motor threshold. To establish the patient motor threshold, we routinely increase the stimulus strength by 5% when stimulating the motor cortex until a visible motor response can be observed in the contralateral hand. For the first time in our experience, we increased stimulus strength to 100%, and no motor response was observed. The procedure was repeated three times. Arbitrarily, we decided to proceed with 65% machine capacity for treatment, since this is the average patient motor threshold in our experience.

A small improvement was noticed within the first 24 hours of the first treatment. For the first time since her admission, Ms. A woke up in the morning, walked to the bathroom, and talked to another patient in her room about her fears of aliens. Ms. A participated in group therapy that morning, but she did not talk. During continued daily transcranial magnetic stimulation, Ms. A's stupor, automatism, and rigidity gradually disappeared. She became able to tend to personal hygiene, to participate in ward activities, and to cooperate with both the staff and her family. Ms. A was willing to spend a day at home, and her family reported a significant improvement. She performed daily activities and smiled occasionally, although she remained mute for another month while taking haloperidol (3 mg daily) before full remission of psychosis.

This case appears to illustrate an ECT-like effect of right prefrontal transcranial magnetic stimulation in catatonic schizophrenia. The extremely high motor threshold to transcranial magnetic stimulation in this catatonic patient should be investigated in other patients.

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Olanzapine Overdose Cause of Acute Extrapyramidal Symptoms

TO THE EDITOR: As one of the atypical antipsychotic agents, olanzapine has been considered to be similar to clozapine but free of the risk of agranulocytosis. The in vitro binding of olanzapine to dopamine (D_1, D_2, D_4), serotonin (5-HT_{2a}, 5-HT_{2c}), α-adrenergic, histamine, and muscarinic receptors is comparable to the binding of clozapine (1). Neuroimaging studies have shown that the D_2-receptor binding of olanzapine in therapeutic doses is similar to that of clozapine (2). Such preclinical studies would predict that olanzapine and clozapine are similar in their lack of propensity to cause extrapyramidal symptoms. Broad-based clinical trials have found that olanzapine, in doses up to 20 mg/day, produces extrapyramidal symptoms at rates approximating those of placebo (3). Sheitman et al. recently reported that olanzapine becomes more distinct from clozapine and is associated with more extrapyramidal symptoms at doses above those most

often prescribed (20mg/day) (4). We present the first reported case in which an overdose of olanzapine produced acute extrapyramidal symptoms.

Quentin, a 9-year-old boy who weighed 64 lb and had no prior exposure to psychotropic medication, took 100 mg of his mother's olanzapine and an indeterminate amount of acetominophen in an apparent suicide attempt. At presentation in the emergency department about 2 hours after ingestion, Quentin was combative and unable to follow commands. He also had tachycardia, hypotension, and decreased gastrointestinal motility. He was treated with elective intubation for airway management and with intravenous fluids and norepinephrine for pressure support. Activated charcoal and *n*-acetyl cysteine were used to prevent further drug toxicity. Cisapride, ondansetron, and metoclopramide were given for promotility effects. Significant laboratory abnormalities during his hospitalization included peak levels of the following: acetaminophen (158 μg/ml), aspartate aminotransferase (93 U/liter), alanine aminotransferase (47 U/liter), and lactate dehydrogenase (434 U/liter). Quentin's platelets were elevated (502,000/mm^3). Quentin did well with treatment and was extubated within 15 hours of admission. By about 36 hours after ingestion and after resolution of his presenting symptoms Quentin developed "jitteriness" and hyperreflexia followed by tremors of the extremities, cogwheel rigidity, a stiff jaw, oculogyric signs, and severe dystonia of the neck. These symptoms were treated with intravenous diphenhydramine for 24 hours and then with oral diphenhydramine for 9 days thereafter. During the course of this treatment, his extrapyramidal symptoms improved significantly. At 13 days after ingestion, Quentin had only a slight upper extremity tremor and no subjective complaints.

Hoffman and Donovan have found that in rats, olanzapine, like risperidone, loses its atypical properties in higher doses by producing catalepsy, not unlike haloperidol at therapeutic doses (5). This effect was not observed with clozapine at any dose, suggesting that clozapine remains unique in its lack of association with extrapyramidal symptoms relative even to the newer atypical antipsychotics.

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Suicide Attempts Among Seropositive Women in New York City

TO THE EDITOR: Among men with AIDS, rates of suicides up to 66 times higher than in the general population have been reported (1–4). Relative risks for suicidal ideation and attempts among seropositive men also are high (5, 6). Suicidality in this population is related to younger age, later stage of HIV disease, more physical symptoms, higher levels of depression, and less social support (4, 6, 7).

Because suicide attempts are three times higher among women than among men in the general population (8), we would expect even higher suicidality among seropositive women than among seropositive men. However, the limited published data suggest otherwise. Among 43 women in the Air Force, none reported suicide attempts, gestures, or plans since testing seropositive (9). Among 55 pregnant women with HIV at an outpatient obstetric clinic, 9% had attempted suicide at some point in their lives (10).

In addition to relative risk of suicide, it is important to know if an HIV diagnosis among women acts as an "inducer" or "accelerator" of suicide attempts. That is, does the seropositive diagnosis lead directly to suicide attempts, or are attempters at risk on the basis of their pre-HIV history (2)? In support of the accelerator argument, most suicide attempts among the HIV-infected occur among those with a psychiatric history, previous attempted suicides, or drug dependence (1).

We surveyed 230 seropositive women from New York City. Their median age was 39.3 years, 83% were Latina or African American, and 44% were high school graduates. Time since testing positive varied from 3 months to 15 years (median=4.3 years), and 24% reported an AIDS diagnosis. Sixty-six percent reported heavy crack or injection drug use at some point in their lives; 19% had used drugs in the last month. In response to two yes-or-no items, the women indicated if they had tried to end their own lives at any time before their HIV diagnosis and at any time since.

Results indicated that 26% of the total group had attempted suicide before their HIV diagnosis; 19% had done so since. Although 58% of those who attempted suicide after the diagnosis had attempted before as well (supporting the accelerator position), the rest, who first attempted suicide some time after their diagnosis, raise potential support for the inducer theory. Consistent with findings among seropositive men, women who had attempted suicide after their HIV diagnosis (compared with those who had not) were younger ($t=3.47$, $p<0.05$) and reported more disease symptoms ($t=-2.35$, $p<0.05$); depression ($t=-2.67$, $p<0.001$), loneliness ($t=-3.12$, $p<0.005$), and need for support ($t=-3.46$, $p<0.005$). Lifetime and current drug use were not significant correlates, but Latina women were more likely than others (26% versus 13%) to have attempted suicide after their HIV diagnosis ($\chi^2=5.80$, $p<0.05$).

Our findings highlight the heretofore unreported high risk of suicide attempts among seropositive women. Of course, the risk is probably multiply determined in this poor, inner city sample. Additional data with adequate controls and more detailed assessment are needed to further explore the inducer versus accelerator debate and to refine the profile of seropositive women most at risk for suicide attempts.

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Gabapentin Treatment of Alcohol Withdrawal

TO THE EDITOR: While benzodiazepines have been the primary treatment modality for alcohol withdrawal, a growing number of preclinical and clinical studies suggest that the anticonvulsants may represent desirable alternatives (1). We report on the use of the anticonvulsant gabapentin in the treatment of alcohol withdrawal in six patients.

Patients were initially assessed for need of emergent inpatient detoxification on the basis of evidence from an intensive history and physical examination. Patients were felt to be candidates for outpatient detoxification if they had no major medical illnesses, had a significant other to provide transportation, and agreed to be seen daily during the detoxification period. Consenting patients included four men and two women with an average age of 39 years. Three of the six had a history of prior medical detoxification with benzodiazepines, five of the six had experienced alcohol blackouts, and two had histories of alcohol withdrawal seizures. The severity of alcohol withdrawal symptoms was measured by the Clinical Institute Withdrawal for Alcohol Scale-Revised (2). On this scale, a score of 10 or higher indicates moderate withdrawal. The average initial score on the alcohol scale for our six patients was 17 (range: 10–27).

The gabapentin dosing schedule was 400 mg t.i.d. for 3 days, 400 mg b.i.d. for 1 day, and then 400 mg for 1 day. Scores on the alcohol withdrawal scale over four daily visits decreased from an average of 17 on day 1 to averages of 11, 2, and 0, respectively. Patients were started on a regimen of medication during the afternoon on day 1 and instructed to take two doses of medication that day. We feel that if three doses had been taken, the scores on the alcohol withdrawal scale on day 2 might have been lower. No adverse effects were noted, and the only complaint was initial sedation by one patient.

Gabapentin is an anticonvulsant approved by the Food and Drug Administration as an adjunct agent for the treatment of partial seizures with or without secondary generalization. In the field of psychiatry, it has recently generated interest as a potential treatment for behavioral dyscontrol and bipolar disorder (3). Gabapentin is not metabolized in humans, does not bind to plasma proteins or induce hepatic enzymes, and is eliminated by renal excretion as an unchanged drug (4).

Taken together, these data suggest that gabapentin may be a compound worth screening as a potential treatment for alcohol withdrawal. More conventional detoxification strategies may need consideration in patients at imminent risk of withdrawal seizures of delirium tremens. However, given gabapentin's lack of drug-to-drug interactions, lack of cognitive impairment, lack of abuse potential, and renal excretion, the potential for use in a variety of detoxification settings is great.

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Behavioral Complications Associated With Donepezil

TO THE EDITOR: Donepezil is a second-generation cholinesterase inhibitor indicated for the treatment of cognitive symptoms of Alzheimer's disease. Some authors suggest that cholinomimetic treatment may also benefit certain behavioral problems associated with Alzheimer's disease such as apathy, psychotic symptoms, and agitation (1). However, another cholinomimetic agent, tacrine, has been associated with behavioral disturbances in some patients with Alzheimer's disease (2).

We report on seven patients with Alzheimer's disease who experienced behavioral worsening following the initiation of donepezil. All were diagnosed with Alzheimer's disease according to DSM-IV criteria. Their mean age was 76.4 years, and their mean score on the Mini-Mental State examination (3) was 18.4. Five patients had experienced dementia-related delusions and irritability before donepezil use; one had a history of major depression; and the other, a history of somatization disorder. At the time of donepezil initiation, four were being treated with sertraline, one with paroxetine, one with venlafaxine, and four with risperidone. All began a regimen of donepezil, 5mg/day. After 4–6 weeks, the dose of five patients was increased to 10 mg/day of donepezil. In the other two cases, donepezil was discontinued after 5 weeks, in one case because of gastrointestinal symptoms and in the other because of increasing agitation. After an average of 7.3 weeks (range: 1–13 weeks) following initiation of donepezil, all seven patients experienced a recurrence of previous behavioral problems. Five became more agitated, one became depressed, and the patient with somatization disorder be-

came more anxious and somatically preoccupied. An additional case (not evaluated by us) came to our attention: a demented nursing home patient, after starting donepezil, resumed playing the piano but also resumed trying to leave the nursing home, a behavior that had resolved as her dementia progressed.

This return of behavioral disturbances is particularly noteworthy in light of the commonly heard expectation that donepezil, like tacrine, may improve cognition by "turning back the clock" by approximately 6–12 months in patients with Alzheimer's disease. However, turning back the clock in Alzheimer's patients with behavioral disturbances may not, in fact, be a desirable outcome, since behavioral problems seen earlier may return. Alternatively, donepezil may improve apathy related to Alzheimer's disease, giving patients more energy and initiative to resume their disruptive behavior. Finally, it is possible that the behavioral symptoms we observed were the result of a drug-drug interaction. However, donepezil is not known to be a potent enzyme inhibitor and is metabolized by means of both the CYP 2D6 and 3A4 hepatic microsomal enzyme systems, making such interactions less likely. Also, a similar pattern of behavioral changes (e.g., regression to an earlier behavioral problem) was seen regardless of the particular agent used in conjunction with donepezil, suggesting that this effect is unlikely to be related to a pharmacokinetic interaction.

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Atypical Neuroleptic Malignant Syndrome and Atypical Antipsychotics

TO THE EDITOR: There has been pronounced variation in the incidence of neuroleptic malignant syndrome over the last 20 years. Neuroleptic malignant syndrome was considered rare in the 1960s and 1970s until several retrospective studies were published. Thereafter, interest intensified, and reports of "atypical" *formes frustes* and incipient neuroleptic malignant syndrome (none of which met diagnostic criteria) appeared in the literature (1). However, later prospective studies, which cited incidence rates for neuroleptic malignant syndrome between 0.07% and 0.15%, confirmed that this is indeed a rare (but certainly not-to-be-overlooked) condition. The recent decline in incidence may, in part, be attributable to more judicious use of conventional antipsychotic medication (e.g., cessation of rapid neuroleptilization, better hydration of patients during titration of medication) (2). In addition, heightened clinical awareness, careful investigation to rule out alternative diagnoses, and greater diagnostic specificity are also major contributory factors. The recent report by Newman and colleagues (3) of atypical neuroleptic malignant syndrome with risperidone adds to an accruing literature on the syndrome with the use of novel antipsychotics but, in our opinion, complicates further this diagnostic conundrum. The spectrum concept of neuroleptic malignant syndrome, dubious at best, is particularly tenuous in treatment with novel antipsychotics (4). Several of the side effects typically observed in the initial titration period with novel antipsychotics (autonomic dysregulation; benign hyperthermia with clozapine) resemble manifestations of neuroleptic malignant syndrome (4). In another example, a recent prospective study of 37 patients receiving clozapine reported elevations of creatine phosphokinase (range: 725–20,000 IU/liter) in 29 patients who were without any other evidence of neuroleptic malignant syndrome (5). Collectively, these observations should be cause for caution in hastily ascribing a diagnosis of neuroleptic malignant syndrome during treatment with novel antipsychotics. At the present time, our understanding and diagnostic specificity for neuroleptic maignant syndrome is too rudimentary to advance the notion of a clinical spectrum, particularly in the context of atypical antipsychotics.

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Schizophrenia and Intellectual Decline

TO THE EDITOR: Ailsa J. Russell, M.Sc.Clin.Psych., and colleagues reported on the WAIS-R test results of adults with schizophrenia who had been previously tested as children (1). They interpreted their results as suggesting "stable impairment" and provocatively entitled their paper "Schizophrenia and the Myth of Intellectual Decline." Because this "myth" was based on numerous empirical studies, it is important to examine the methodological details of the study by Russell et al. to reconcile the apparent contradictions. There are five major reasons to doubt their conclusions and to infer that the appearance of stability is, instead, likely evidence of intellectual decline.

1. The WAIS-R short form used on the second testing occasion probably overestimates the full-scale IQ of schizophrenic patients because it does not include several subtests on which poor performance is common among this group. To address this issue empirically, I examined the WAIS-R performance of 103 schizophrenic patients at the National Institute of Mental Health. The group's mean full-scale IQ was

88.3 (SD=11.9) with a score of 97.5 (SD=88.3) on the Wide-Range Achievement Test-Revised; those scores suggested a 9.1-point decline (matched pair t test: t=8.15, df=102, p< 0.0001). The patients' performance on Russell et al.'s five-subtest short form (mean=8.77, SD=2.2) differed significantly (t=6.53, df=102, p<0.001) from their performance on the remaining six subtests (mean=8.02, SD=1.9), and as well as on all 11 subtests (mean=8.40, SD=2.0). This significant difference occurred despite a high correlation (r=0.94) between short-form and full-scale IQs. Thus, subjects retained their relative positions across short-form and full-scale IQs, but the short-form estimates were systematically higher than the actual full-scale IQs. Because all WISC-R subtests were administered at time 1, the comparison of actual WISC-R full-scale IQ versus short-form WAIS-R IQ is biased against detecting differences.

2. Age cohort effects confound the use of WISC-R and WAIS-R scores to determine the longitudinal course of intellectual functioning. As reviewed by Kaufman (2), each restandardization of the major IQ tests has documented substantial "gains" in IQ, estimated at 3 points per decade in the United States, where the IQ tests were normed. This cohort effect influences examinations of individual performance over time: the WISC-R was published in 1974; the WAIS-R, in 1981. At time 1, the group was 13.3 years old; their IQs were calculated relative to those of persons born in 1961. At time 2, the group was 32.9 years old; their IQs were calculated relative to those of individuals born in 1948. This 13-year age difference is likely responsible for a 3–4 point WAIS-R advantage relative to the WISC-R. In addition, the WAIS-R norms for 16- to 19-year-olds have been criticized as producing spuriously high scores (2). At time 2, at least one subject fell in this age range (table 2, minimum age=17). Again, the psychometric problem decreased the probability of documenting intellectual loss.

3. Several studies reviewed by Kaufman (2) have suggested that WAIS-R scores of intellectually limited subjects are systematically higher than their WISC-R scores, with differences as high as 11 points reported. Thus, evidence of equivalent WISC-R IQ and WAIS-R IQ may be evidence of actual IQ decrement among these subjects. Russell et al. included six to seven subjects with WISC-R IQs lower than 75; the inclusion of such intellectually limited subjects would be particularly problematic and raise possible diagnostic issues.

4. As noted by Russell et al., their group was highly unrepresentative of schizophrenic patients. The subjects had childhood-onset psychiatric symptoms, low overall IQs, and a substantial number of childhood-onset psychoses. What, if any, is the possible justification for generalizing the findings of Russell et al. to schizophrenic patients as a whole, as implied by the title?

5. The inclusion of nine subjects who were psychotic at time 1 undermined any examination of decline related to onset of psychotic illness, confusing this issue with deterioration over illness course. The fact that these subjects did not differ significantly from the rest of the group at time 1 or time 2 (a comparison with remarkably limited power) is not relevant to the main argument. The question of intellectual decline over illness course is distinct from the question of loss of intellectual ability with illness onset. Furthermore, the deletion of these nine subjects would have reduced the group to 25, a small number to use to dispel a myth confidently.

In summary, there are several reasons to suspect that the present comparison of estimated WAIS-R scores and WISC-R scores in schizophrenic patients resulted in the appearance of stability when actual loss, obscured by psychometric confounds, occurred. Considering that a decline of 2.3 points was documented without the contribution of these likely artifacts, a true decline of 8–10 points, the extent of decline estimated by using a variety of methods, may actually have been present.

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TO THE EDITOR: Russell and colleagues have made an important contribution to the literature on intellectual functioning in patients with schizophrenia. However, their claim that intellectual decline is "a myth" overstates the case. The first problem is one that the authors partially acknowledge, namely, the biased nature of their study and, hence, the lack of generalizability. Their own data from a *representative* population-based cohort (1) show that the premorbid IQ deficit in children who later develop schizophrenia is one-third of a standard deviation (i.e., around 5 IQ points). Equivalent figures from a later U.K. national cohort suggest that the deficit may be around one-half of a standard deviation (i.e., 8 IQ points) (2), as do the data from the Swedish conscript cohort (3). The mean childhood IQ of their current group was 84.1, that is, just over one standard deviation below the mean. Hence, it is *not* representative of preschizophrenic children.

The next problem is the lack of control for a period effect, that is, changes in IQ in the population over time. Evidence from the United States shows that children's intelligence has increased by approximately 3 points per decade since the 1930s (4, 5), and anecdotal reports from the United Kingdom suggest similar trends in educational attainment. IQ tests standardized at the same time but employed years apart should reveal an increase.

In addition, research with groups with mild and moderate learning disability (6–9) shows that subjects tested on the WISC and later on the WAIS (or their revisions) consistently show an apparent improvement due to psychometric properties of the scale, separate from the period effect. Hence, the lack of increase (or the slight decrease) in scores reported by Russell et al. masks a larger decrease in IQ over the follow-up period. Such a decrease is suggested by well-controlled, albeit cross-sectional, studies of first–onset cases (10) in which schizophrenic patients' cognitive measures are more than one to two standard deviations below the control mean.

Finally, a difficulty arises in the comparison of results from the WISC-R and the WAIS-R. Russell et al. quote correlation coefficients between the two scales, but this is misleading. There would be a perfect correlation between the scales even if one were consistently 10 points higher than the other. We need to know the slope of the regression line and its intercept.

So what do we know for sure about IQ and schizophrenia? There is a slight reduction in the average IQ of children and young people who later develop schizophrenia. It is likely that there is a further reduction between childhood and the first onset of the disorder, although truly longitudinal data on this point are sparse. Whether there is a further deteriora-

tion in intellect in most cases over the course of the disorder is still an open question.

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TO THE EDITOR: In their study, Russell and colleagues present follow-up IQ measures for 34 adults with schizophrenia who had had initial IQ measurement 20 years earlier when they were referred to a child psychiatry clinic for a variety of psychiatric disorders. Comparing the *averaged* IQ scores for the adult patients with schizophrenia with their own *averaged* IQ as children, Russell et al. report that the individuals included in their study initially showed an impairment in general intellectual function and that there was no significant difference between the patients' averaged childhood and adult IQs. The authors conclude that their findings are consistent with the neurodevelopemental concept of schizophrenia and that a lesion occurring during early brain development may be responsible for both the childhood and adult cognitive impairment of patients with schizophrenia.

One may quarrel with many aspects of this report of Russell et al., e.g., the nonrandomness of the group on which their statistics are based (one-third of the original group was excluded because they did not have the second [adult] IQ examination) and, indeed, the question of whether the sample of the schizophrenic population from which the cohort was drawn was representative. Most adult patients with schizophrenia do not have 1) a history of referral to a psychiatry clinic as children or 2) childhood IQs one to two standard deviations below the norm, as did one-third of this group. Moreover, the IQs of those included were 14 points below the scores of those not tested a second time and, hence, excluded from the sample). However, except for their choice of title and the final paragraph of their discussion, Russell and colleagues are appropriately modest in making claims for generalization of their findings. The authors are also to be commended for reporting not just their summary statistics but graphic representation of the data thus summarized (a numerical table would be even better, as it is possible to determine IQs of only 19 of the 34 individuals represented on the graph). It would be useful if all journal editors required authors to report similarly, to the extent possible, the actual data that their statistics summarize.

Even if they reject the evidence that cognitive impairment follows onset of the illness in many (but by no means all) patients with schizophrenia as reported by most investigators from Kraepelin (1) onward (2, 3), the data presented by Russell et al. fail to support their conclusion that "the deficit in intellectual function observed in these patients, and reported in the literature, is lifelong and predates the onset of schizophrenia." In contrast to the majority of adults with schizophrenia, for whom the premorbid intelligence and mental statuses are within normal limits (2), the mean childhood IQ score for the cohort of Russell et al. was 82.4; as children, at least 10 patients had IQs below 80, and 38% were diagnosed with psychotic disorders. Of 10 patients with IQs below 80 at the childhood examination, the IQs of only two declined, and the IQs of seven increased at follow-up. In contrast, five of six patients with initial IQs of 100 or above had a *decrease* in IQ of 10–20 points between the first examination and the second 20 years later. Averaging the scores from the first examination for all the patients and comparing these scores with averaged scores from the second examination 20 years later yielded an almost unchanged mean score for the entire cohort at follow-up. The authors suggest this is an example of "regression to the mean." However, a decline of IQ by 15–20 points between late childhood and adult life is not a usual occurrence and requires a nonstatistical explanation. Moreover, their regression analysis found that the time 1 IQs explained only 60% of the variance in time 2 IQs, even after they corrected for age, sex, and so forth; this finding leads to the inference that something else, perhaps schizophrenia, played a role here.

The article of Russell et al. provides an excellent example of why the usual statistical measures of central tendency are not sufficient in this domain (4). Pooling and averaging data of heterogeneous groups obscures the scientifically interesting findings in this report. The fact that IQs increased for some patients, stayed about the same for others, and declined for another subgroup indicates the need for inquiry into why these differences occur. There is also the question of the relationship of IQ changes to treatment. As Wyatt (5) and others have reported, neuroleptic treatment of schizophrenia may decrease the decline in cognitive faculties formerly associated with this illness. It would be of great interest to explore the role that both original psychiatric diagnoses and time and type of treatment may have played in these very different trajectories of the schizophrenia syndrome.

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Drs. Russell and Murray Reply

TO THE EDITOR: In his letter, Dr. Gold puts forward five points from which he concludes that the "appearance of stability" in IQ in our subjects is actually "likely evidence of intellectual decline." We discussed three of Dr. Gold's points in our original paper; the remaining two are matters of test artifact.

1. Dr. Gold points out that we included six to seven subjects with IQs less than 75 and raises the issue of comparing WISC and WAIS scores among subjects termed "intellectually limited." The cutoff for "intellectually limited" is usually a full-scale IQ lower than 70. We have, therefore, reexamined our data in subjects whose full-scale IQs were lower than 70. During the follow-up period, 50% of these subjects showed improved IQ, and 50% showed a decline. There were no significant differences between IQs at time 1 and time 2 in the subjects whose full-scale IQs were lower than 70, a finding similar to the findings for the group overall. Thus, there is no substance to this point.

2. Dr. Gold and Dr. David raise the issue of the short form of the WAIS-R. There are considerable available data concerning the reliability and validity of the five-subtest short form of the WAIS-R; these are discussed in our original paper. Advantages of the short form are that it 1) omits several of the subtests (e.g., information and arithmetic) that assess educational attainment and 2) avoids tests (e.g., those requiring the subjects to accurately name five prime ministers of Great Britain since World War II) that would be affected by a long period of serious mental illness. In using this form, we also considered issues of test fatigue in patients who, in general, remain chronically unwell (1).

Dr. Gold also refers to data he has collected on adults with schizophrenia. His results confirm that equivalent IQs are derived 1) when 10 subtests of the WAIS-R and 2) just five subtests are administered; however, the former produces a lower mean subtest score. Although the difference between the means of the 10 and the five subtest scores reaches statistical significance, in practice such a difference would never be considered evidence of cognitive decline. The IQ literature suggests that a scaled score should be at least 3 points above or below the mean before it can be considered noteworthy (2). Dr. Gold presents scores that are approximately one-third of a scaled score from the mean.

3. Stevens et al. state that in "the majority of adults with schizophrenia . . . the premorbid intelligence and mental statuses are within normal limits" and cite a 1991 study by Frith et al. They highlight the fact that for our group, the mean premorbid IQ is 82.4 with at least 10 subjects having IQ measures lower than 80. Closer examination of the Frith et al. study demonstrates that premorbid IQ was "estimated" retrospectively, after illness onset, by employing a word reading test—the National Adult Reading Test. This test can provide both overestimates and underestimates of IQ (3, 4). Furthermore, Nelson (5) suggests that there are difficulties in using the National Adult Reading Test as a measure of IQ when IQ falls close to the test's basal and ceiling levels. The basal IQ that can be estimated by the National Adult Reading Test is 84, i.e., to make 100% errors on that reading test would provide a full-scale IQ estimate of 84. It can go no lower. It is hardly surprising, then, that the conclusion of studies employing this type of methodology is that premorbid IQ falls within normal limits since the measures they employ mean that it is impossible to estimate IQs lower than 84. The literature indicates that the mean IQ in adult schizophrenic samples is generally lower than the mean of the general population (6); studies estimating premorbid IQ in schizophrenic patients should employ assessment techniques that encompass the full distribution.

4. Stevens et al. also comment on the increases and declines in IQ across the group, a phenomenon that does appear to reflect regression toward the mean; as they point out, the majority of those with low IQs demonstrate an increase, and the majority with higher IQs demonstrate a decline. They suggest, however, that such individual variation requires a nonstatistical explanation. Certainly, there are many possibilities; as stated in our original paper, changes in another cognitive function such as memory, orientation, attention, or frontal function may account for this. The WAIS-R summary IQ is a rough index to the general functioning of an individual and is a composite score of a number of abilities and skills. It is also possible that interrupted education was at play in this group. IQ tests are heavily dependent on acquired knowledge and can often be viewed as tests of educational attainment. A proportion of our subjects were hospitalized early in life. One could hypothesize that their ability to benefit from their educational experiences was, at best, heavily compromised.

5. We do agree with our colleague Dr. David that one must be cautious in interpreting longitudinal data, but we would point out that such a design does control for most of the age cohort effects that plague cross-sectional studies.

6. Dr. David is, of course, correct that the group we studied is unusual in that the schizophrenic subjects had already been sufficiently deviant as children to be referred to a child psychiatry department. We did not claim that they were representative of all schizophrenic patients but pointed out that, as he knows, all four recent cohort studies that examined childhood IQ in representative samples of preschizophrenic patients found it to be significantly reduced.

In summary, the evidence is now conclusive that children who go on to develop schizophrenia have lower-than-average IQs. Dr. David believes that there then ensues further decline, although he acknowledges that "truly longitudinal data on this point are sparse." If he and our other correspondents wish to continue to believe in this "myth" of further decline, that is their right. If they wish the rest of us to share their belief, they must produce convincing longitudinal data.

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Fluoxetine and Norfluoxetine

TO THE EDITOR: The article by Jay D. Amsterdam, M.D., and his colleagues (1) on fluoxetine plasma levels was impressive and interesting. The authors, however, state that "it is possible . . . that a lower dose would have shown a threshold effect" (p. 967). I think it would be more accurate to say, on the basis of elementary pharmacology, that a lower dose would *have* to show a threshold effect if the medication is, in fact, effective; an ineffective dose might be 1 mg or 1 molecule, but there has to be a dose that is too small to be effective. This is not an empirical issue, and one cannot question the fact that an ineffective dose would have been found had the authors used lower doses.

In fact, the scattergrams the authors present suggest that they may have found evidence of an ineffective dose, but this was obscured by the fact that the vast majority of patients were above the threshold needed for effectiveness. The authors might evaluate the relationship between plasma levels and benefit by looking only at patients with plasma levels below 100 (or 150) ng/ml.

Without any evidence of a threshold effect, the authors' data would suggest that there is no reason to increase the dose of fluoxetine above 20 mg/day. As the authors indicate, however, there is some evidence that higher doses are helpful for some patients; I think it's fair to say that even if only five patients out of 100 would benefit from an increased dose of fluoxetine, this would be of some clinical (although perhaps not statistical) significance. Of note, the authors did not specify whether any patients dropped out of the study before completing the 8 weeks on a regimen of 20 mg/day because of an inadequate response.

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JEFFREY A. MATTES, M.D.
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Dr. Amsterdam and Colleagues Reply

TO THE EDITOR: Dr. Mattes has raised several issues involving both plasma concentration and dosage. As suggested in our paper, one possible reason we failed to detect a minimum therapeutic fluoxetine plus norfluoxetine plasma concentration is that the 20-mg fixed dose yielded a distribution of concentrations whose lower tail exceeded the minimum therapeutic plasma concentration. Fluoxetine dosing studies argue against the possibility that this potential problem actually affected our results.

A body of data suggests that 20 mg/day of fluoxetine does not substantially exceed a minimum therapeutic dose and that some patients require higher doses. Although some data suggest that 5 mg/day can be efficacious (1), two studies support the efficacy of 20 mg/day (2), and a fixed dose of 20 mg/day has been associated with a numerically greater response rate than a fixed dose of 5 mg/day (1). Further, a fixed dose of 40 mg/day has yielded a numerically higher response rate than a fixed dose of 20 mg/day (2). Recent findings indicate that in patients unresponsive to an initial trial of 20 mg/day (when that initial trial is of sufficient length to distinguish between time and dose effects), a dose increase to 60 mg/day results in a superior therapeutic response (3). Therefore, a dose of 20 mg/day should result in a distribution of plasma concentrations that would include a minimum therapeutic plasma concentration, provided one exists and can be detected.

Dr. Mattes has suggested that our formal analytical methods should be applied to that subset of data where concentrations are lower than 100 (or 150) ng/ml. Visual inspection of figures 1 through 3 indicate that the distribution of efficacy parameters associated with plasma concentrations within the range of 0–150 ng/ml is virtually random. Furthermore, 102 of the 615 (16.6%) observations included in these data and our analyses are of concentrations lower than 150 ng/ml.

We disagree with Dr. Mattes that our "data would suggest that there is no reason to increase the dose of fluoxetine above 20 mg/day." Rather, these data suggest that nonresponse to 20 mg cannot be meaningfully assessed by examining plasma concentrations. With respect to early discontinuation, data from patients who discontinued for any reason earlier than 8 weeks could potentially confound time and concentration effects; these data were, therefore, not included.

We agree with Dr. Mattes that from a logical perspective, a minimum efficacious dose and plasma concentration must exist on an individual patient basis. The results of our analyses, however, imply that these individual values vary considerably from one patient to another. From a clinical perspective, the issue is whether a common minimum therapeutic plasma concentration exists for a large group of patients and whether plasma concentration information can guide decisions about the adequacy of drug dose for individual patients. Our results indicate that this is not the case for fluoxetine.

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Delirium Following Cessation of Alcohol Consumption

TO THE EDITOR: David Hersh, M.D., and his colleagues presented an excellent review of persistent delirium following the cessation of heavy alcohol consumption (1). There are a few areas, however, that deserve further clarification.

1. The authors make a determined effort to note that the patient presented in their case report demonstrated persistent "delirium" and not "delirium tremens," the latter requiring the presence of tremors and autonomic hyperactivity. Elsewhere in their review, however, this distinction becomes murky. The authors state that "although delirium tremens typically remits over a period of several days, cases persisting for weeks have been reported" (p. 846). In fact, the reference they cited concerns "alcohol withdrawal delirium" (2), not delirium tremens. It appears that it is *only* the delirium, not the autonomic hyperactivity and tremors, that may be protracted following heavy alcohol consumption.

2. Citing Nordstrom and Berglund (3) and Koch-Weser et al. (4), the authors report that "approximately 5% of patients hospitalized for alcohol withdrawal go on to develop delirium tremens" (p. 846). There is no recent empirical evidence to support this observation. The study by Nordstrom and Berglund (3) used data obtained from 1949 to 1969 and defined delirium tremens as "an alcohol withdrawal syndrome with hallucinosis and a clouded sensorium." This definition is not consistent with modern terminology for delirium tremens. The Koch-Weser et al. report (4) obtained the 5% figure from a 1966 article by Victor (5), which, in turn, had obtained the number from a 1953 article (6). The latter article reported that 5% of 266 consecutive patients admitted with obvious alcoholic complications experienced "typical delirium tremens."

In my experience, delirium tremens is observed *only* in patients who are not aggressively and appropriately treated for the preceding alcohol withdrawal syndrome.

3. The authors state that the ideal benzodiazepine for treating alcohol withdrawal has an intermediate half-life. This claim is not referenced. Sellers et al. (7) have described a symptom-triggered protocol for the treatment of alcohol withdrawal with the long-acting benzodiazepine, diazepam. The advantages of using this paradigm include being able to initially "load" patients in severe withdrawal, reducing the need for later dosing, and permitting a withdrawal relatively free of cyclical variations, from drug-induced "highs" to the reemergence of withdrawal symptoms (8). Saitz et al. (9) have elegantly demonstrated that this dosing paradigm, which uses a long-acting benzodiazepine, dramatically shortens both the total dosing period and the total dose of benzodiazepine required for treatment.

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TO THE EDITOR: In their clinical case conference, Dr. Hersh and his colleagues describe a 40-day interrupted hospitalization of a 71-year-old man with a severe alcohol history who was admitted to an academic medical center for alcoholism. On day 4 of a withdrawal treatment schedule, the patient developed a delirium that progressively worsened. He was treated with thiamine, chlordiazepoxide, and, eventually, haloperidol for severe agitation. On the 18th day, his score on the Mini-Mental State was 23 of a possible 30, and he was transferred to a rehabilitation facility. He relapsed quickly, however, and was returned to the academic center where conservative treatment with the same medications was continued for an additional 2½ weeks. At the time of discharge, he was still not fully recovered.

Had this patient been treated in Denmark or Sweden, he would have been a candidate for ECT (1). Admittedly, the literature reviewed by Strömgren is sparse. Considering the life-threatening nature of such deliria, as well as the risks of neuroleptic malignant syndrome with the administration of neuroleptics, especially haloperidol, it is reasonable to consider ECT. There is a need for a collaborative study of the merits of ECT in drug-related deliria.

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Dr. Kranzler and Colleagues Reply

TO THE EDITOR: We thank both of the authors who commented on our recently published clinical case conference. We agree that the literature on alcohol withdrawal delirium is inadequate to address a number of important clinical issues. As Dr. Adinoff correctly points out, data on the prevalence of delirium tremens are from an earlier time, and in light of therapeutic developments, the 5% figure quoted in the introduction would represent the upper bound for prevalence. As pointed out by Dr. Fink, the use of ECT to manage alcohol withdrawal delirium, although of potential value, lacks empirical evaluation. We are pleased that our case review has helped to highlight the need for systematic study of alcohol withdrawal delirium and delirium tremens.

We agree that although the distinction is often not made clinically, it is important to differentiate alcohol withdrawal delirium from other symptoms in delirium tremens, since autonomic hyperactivity does not follow the same time course as does the delirium. As regards the choice of a benzodiazepine for treatment of alcohol withdrawal, we believe that lorazepam or oxazepam, which have an intermediate duration of action, is preferable to longer-acting benzodiazepines for

two reasons. First, they do not require hydroxylation, so that in the context of hepatic dysfunction, they will not accumulate to toxic levels. Second, and more important, since treatment of alcohol withdrawal is increasingly being done in an ambulatory setting, the use of a long-acting benzodiazepine may be problematic: it has a greater risk for additive sedation if alcohol is consumed concurrently. Finally, the clinical experience of Dr. Adinoff notwithstanding, it is not clear that in all cases, the aggressive treatment of early alcohol withdrawal can prevent the development of delirium tremens. The fact that delirium tremens can have its onset in the absence of early withdrawal symptoms argues against a simple progressive model for all cases of alcohol withdrawal. Clarification of these important clinical issues will also depend upon systematic empirical investigation.

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Risk Factors for Neuroleptic Malignant Syndrome

TO THE EDITOR: Perminder Sachdev, M.B.B.S., M.D., Ph.D., F.R.A.N.Z.C.P., and colleagues (1) reported in a case-control study that ECT was a risk factor for neuroleptic malignant syndrome in their patient group. Since ECT has been used effectively to treat neuroleptic malignant syndrome (2), it seems quite unlikely that it could be causally related to subsequent development of the syndrome. I offer the following speculation about a correlational (as opposed to a causal) relationship between ECT and neuroleptic malignant syndrome. The patients in the group of Sachdev et al. who developed neuroleptic malignant syndrome were agitated and received large early parenteral neuroleptic doses. Even though the authors indicated that the comparison group was matched for diagnoses, it is possible, and even likely, that patients with a broad range of psychopathology were clumped into the same diagnostic groups. Thus, a group of "schizoaffective" patients may have vastly different current or past symptom pictures. Since patients with manic symptoms respond well to ECT, it could be that the patients in the group with neuroleptic malignant syndrome were thus more likely at some point in their illness course to have had ECT.

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TO THE EDITOR: We noted with interest the report by Sachdev et al. This retrospective study identified agitation, increased neuroleptic dosage, and history of ECT as risk factors for neuroleptic malignant syndrome. The clinical overlap of neuroleptic malignant syndrome and catatonia (1–3) prompts us to seek clarification related to catatonia.

The authors used catatonia as one of the possible subcriteria for diagnosis of neuroleptic malignant syndrome but did not report how many of the 25 patients or 50 comparison subjects showed catatonic signs. This is especially relevant since their definition of agitation as "excessive and purposeless motor activity" (p. 1156), which they found to be a risk factor for neuroleptic malignant syndrome, matches the published definitions for catatonic excitement (4, 5). DSM-IV and other diagnostic criteria (4) accept a single motor sign as sufficient to diagnose catatonia. The increased risk of neuroleptic malignant syndrome reported after administration of neuroleptics to patients with catatonia (1) may be confirmed if Sachdev et al. have data on catatonic signs in their neuroleptic malignant syndrome cases.

The authors also found prior history of ECT as a risk factor for neuroleptic malignant syndrome. Perhaps this also relates to catatonia, since this syndrome may be recurrent (6) and the patients with neuroleptic malignant syndrome may have had prior ECT, a common treatment for catatonia (7).

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Dr. Sachdev Replies

TO THE EDITOR: I thank Dr. Rasmussen and Dr. Francis and his colleagues for raising important issues in relation to our study. For the diagnosis of catatonia, we needed the presence of one of the following: mutism, extreme negativism, peculiarities of voluntary movement (posturing, waxy flexibility, and so forth) or echophenomena. Excessive and purposeless motor activity was in itself not sufficient for this purpose, since we considered establishing "purposelessness" to be an unreliable exercise and excessive motor activity to be a common feature of many psychiatric disorders. Such an approach would underdiagnose catatonic excitement, which we accepted as a limitation of a retrospective study. Catatonia was diagnosed in 11 subjects (44%) with neuroleptic malignant syndrome but in only two comparison subjects (4%) in our study. Catatonia was, however, present before the onset of neuroleptic malignant syndrome in only one subject from the neuroleptic malignant syndrome group. Our data, therefore, do not permit us to comment on catatonia as a possible risk factor for the development of neuroleptic malignant syndrome as has been suggested elsewhere (1). We acknowledge that catatonia is an important manifestation of neuroleptic malignant syndrome, and lethal catatonia (2) may be indistinguishable from a severe case of neuroleptic

malignant syndrome. The overlap does suggest some common features in the pathophysiology, but until we understand the pathogenesis of catatonic withdrawal and how that may differ from excitement, this similarity will not yield new insights. That the presence of catatonia may be a risk factor for neuroleptic malignant syndrome is worth examining further, however, as it may urge us to use alternative treatments such as ECT.

The finding of previous ECT as a risk factor for neuroleptic malignant syndrome has excited comment from both groups. In our article, we resisted the temptation to speculate on this finding until it had been confirmed independently. We agree with Dr. Rasmussen that it is, at best, an association that possibly flags the characteristics of the primary psychiatric disorder that prompted treatment with ECT. A prominence of affective symptoms (manic or depressive) or catatonia in the histories of these individuals is distinctly possible, but we cannot present satisfactory data to examine either. Future studies should pay attention to these possibilities.

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Suicide Risk in Schizophrenia

TO THE EDITOR: We read with great interest the excellent article by Hannele Heilä, M.D., and colleagues (1) on the clinical characteristics of suicide victims with schizophrenia in the general population of Finland. One important finding of this study is that suicide may occur at any point during the course of the illness, since three-fourths of the suicides were committed during an active phase. Previous reports, focusing especially on attempted suicide, had led to the general conclusion that active psychotic features were less important than depression and hopelessness in the assessment of suicide risk in schizophrenic patients (2, 3). When we studied the more severe forms of attempted suicide, however, 81% of the schizophrenic subjects presented positive psychotic symptoms at the time of attempting suicide (4). Our study also stressed the importance of previous attempts and the fact that more than one-quarter of the schizophrenic subjects were receiving psychiatric inpatient care when they attempted suicide, a finding similar to those of Heilä et al. (1). Therefore, we believe that clinicians should keep in mind that not only demoralization or depressive symptoms are important in the assessment of suicide risk in schizophrenia, but positive psychotic symptoms are even more significantly related to the risk of a serious attempt or suicide.

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Dr. Heilä and Colleagues Reply

TO THE EDITOR: We thank Dr. Vieta and colleagues for their comments. We agree with the conclusion they have drawn that among persons with schizophrenia, active schizophrenia symptoms are associated with suicide more frequently than are stabilized illness phases with depressive symptoms, a finding that is somewhat at variance with some earlier studies. In our suicide study group, 71% (N=55 of 77) of the suicide victims with schizophrenia had currently prominent (two or more) positive schizophrenia symptoms before suicide. This is in line with the recent research findings (1, 2) suggesting that positive symptoms are associated with heightened suicide risk and that among subjects with prominent negative symptoms, the risk may be low. Regardless of the illness phase, however, the significance of depression in suicides of persons with schizophrenia seems also evident: altogether, slightly more than one-half (N=38 of 74; 51%) of our suicide victims simultaneously had depressive symptoms and prominent positive schizophrenia symptoms. For suicide prevention, assessing and identifying the depressive symptoms among subjects with schizophrenia is important also during the active illness phase of schizophrenia.

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Etiology of Borderline Personality Disorder

TO THE EDITOR: I agree with Mary C. Zanarini, Ed.D., and her colleagues (1) that borderline personality disorder will ultimately be understood as an illness with a multifactorial etiology. In our own work, cited by Zanarini and elaborated in a series of reports (2–4), we have similarly emphasized that childhood sexual abuse is neither necessary nor sufficient for the development of borderline personality disorder but that the patient with this diagnosis has almost invariably emerged from an environment characterized by disordered attachments and histories of affective illness in one or more close relatives.

Earlier studies by Zanarini et al. (5) and others (6–8) support this etiological perspective. Still others (9–14) further

note that a history of sexual abuse, along with a cluster of severely self-destructive behaviors, most accurately characterizes those borderline patients who require hospitalization. Therefore, it is not surprising that for the majority (61.5%) of "severely impaired" inpatients in the study of Zanarini et al. (1), childhood sexual abuse would emerge as a predisposing factor in their illness. Unfortunately, the authors make no comment on the skewed nature of their study group and its possible relation to this finding.

Eagle (15) has issued a general warning regarding the use of this class of restrospective data to establish the etiology of borderline personality disorder. Following Eagle's logic, if researchers were to sample only hospitalized borderline patients, "they would likely develop an etiological theory seriously distorting and exaggerating the nature and strength of the relationship between childhood sexual abuse and adult personality disorder" (p. 134). Such distortion, if unquestioned, can have serious consequences for both research and clinical practice.

Zanarini and colleagues themselves call for a more complex, nuanced understanding of borderline personality disorder. In the absence of prospective developmental studies, a next step might be a careful comparison between predisposing factors in "severely impaired" inpatients like those in the Zanarini group and an equally large sample of outpatients who carry a borderline diagnosis but have not needed hospitalization. Such a comparison would help clarify those factors common to the majority of individuals suffering from borderline personality disorder, and would document the extent to which sexual abuse may be correlated with symptom severity, as opposed to diagnosis per se.

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Drs. Zanarini and Frankenburg Reply

TO THE EDITOR: We appreciate the comments of Dr. Salzman, who brings up the important issue of whether sexual abuse is associated with the etiology of borderline personality disorder per se or only with that of severe inpatient cases of borderline personality disorder. Previous research has found that the rates of childhood sexual abuse are about the same for criteria-defined borderline outpatients and inpatients (1–9). Dr. Salzman and her colleagues, however, found a substantially lower rate of abuse in a group of symptomatic volunteers (10).

Clinical experience suggests that the boundary between outpatients and inpatients with borderline personality disorder is quite permeable, with today's outpatient being tomorrow's inpatient and vice versa. In this regard, it is important to note that studies have consistently found that a substantial percentage of outpatients with borderline personality disorder have a history of prior hospitalization (11, 12).

Thus, Dr. Salzman is highlighting the existence of a third group of patients—mild outpatient cases of borderline personality disorder with no history of psychiatric hospitalization. In our clinical experience, patients with the diagnosis of borderline personality disorder who have never been hospitalized lack the impulsivity of those patients who have been inpatients, since patients with borderline personality disorder are typically hospitalized for their own protection during periods of intense self-destructiveness. This raises the question of whether "borderline" patients who have never been hospitalized are, in fact, borderline at all or whether they should be considered patients with borderline traits or features. To phrase the question another way: should nonimpulsive patients who manifest the intense dysphoria, suspiciousness and dissociation, and difficult, stormy relationships characteristic of borderline personality disorder be considered borderline? Should someone without a history of deliberate physical self-harm, help-seeking suicidal efforts, or both be thought of as a borderline patient?

Further research is needed to untangle these issues. Until that time, we can only reiterate that even in the most severely impaired of borderline subjects, we have found that childhood sexual abuse is neither necessary nor sufficient for the development of borderline personality disorder.

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Science of Addiction

TO THE EDITOR: The editorial by Charles P. O'Brien, M.D., Ph.D. (1), presented an eloquent and cogent call for more psychiatric involvement in and more financial support for the treatment of addictive disorders. Dr. O'Brien's identification of addiction as a chronic disease was, I believe, particularly important.

In this context, one sentence in the editorial concerned me: "A modern conceptualization of addiction is that it acts as a chronic disease produced by thousands of exposures to drugs." This sentence seems to imply that repeated exposure to drugs is a sufficient condition for developing drug addiction and that thousands of exposures are necessary for an addictive pattern of drug use to develop. I believe that neither of these implications accords with our experience. Repeated exposure to drugs typically produces neuroadaptation, which can manifest as tolerance, withdrawal, or both. While neuroadaptation can contribute to maintaining or increasing drug use, most investigators agree that neither tolerance nor withdrawal is necessary or sufficient for the development (or the diagnosis) of drug addiction. Moreover, an explanation of addiction that depends on repeated exposure cannot account for individual differences in susceptibility to addiction: some individuals who are repeatedly exposed to alcohol or other drugs will develop addictive patterns of substance use, while others with similar exposure will not. That a biopsychological vulnerability to developing addiction exists before the onset of substance use is indicated also by findings in longitudinal and archival studies that childhood temperamental disturbances—including high emotionality, low soothability, and impulsiveness—are associated with later development of alcoholism or drug addiction.

If addiction is not produced by exposure, how, then, can we understand its development? In a general sense, I would describe addiction as a chronic condition that develops through a process that involves complex interactions over time between genetic and environmental factors. More specifically, I would propose that two sets of determinants are involved in the development of an addictive disorder: 1) those that concern underlying neurobiological abnormalities that are shared by all addictive disorders and 2) those that relate to the selection of a particular substance as the one that is preferred for addictive use. I would add that each set includes both genetic and environmental factors. Environmental factors in the development of the underlying neurobiological abnormalities include deficiencies in the child's caregiving environment during the first years of life, when the maturing brain is most sensitive to external influences and depends on particular qualities of interchange with the caregiving environment for its healthy development. Genetic factors in selection include genetically based variations in 1) the sensitivity of the reward system to different substances, 2) the body's sensitivity to immediate aversive consequences of using a substance (such as flushing or standing ataxia after ingestion of alcohol), and 3) the intensity of the individual's sensitivity to various painful affects, since the substance that brings relief from the most disturbing affects is thereby associated with the strongest negative reinforcement.

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Dr. O'Brien Replies

TO THE EDITOR: I greatly appreciate the letter of Dr. Goodman because it gives me a chance to expound on the nature of addiction. This is really one of the most complex biopsychosocial problems faced by clinicians. One of the difficulties in conceptualizing this problem is that observers have a tendency to view it from one dimension at a time; addiction requires consideration of multiple, simultaneous, and continuous variables. Dr. Goodman is right on target in pointing out that addiction is much more than just tolerance and withdrawal, although tolerance and withdrawal may be extremely important in any given case.

My own view is more completely expounded in a chapter in the work by Goodman and Gilman (1). Table 24–1, using the model of an infectious disease, lists categories of variables that interact to determine both initiation and continuation of drug use. Among the agent (drug) variables are availability, cost, and purity. Among the host variables are some

of those listed by Dr. Goodman as "genetically based variations." Some of these genetically based variations tend to protect the individual against becoming addicted. For example, the flushing reaction to alcohol would tend to reduce the probability of becoming an alcoholic, yet people with the flushing reaction still can overcome it and become alcohol dependent. On the other hand, the tendency to develop rapid tolerance makes an individual more likely to become an alcoholic (2), but many people who inherit this tolerance totally avoid alcohol because they have seen the devastation that it wreaks among family members. The third category of variables is environmental. Social pressures and approval or disapproval of peers are influential. The current wave of binge drinking in colleges may influence the probability of developing alcoholism among students, but it will not be the sole determinant.

Thus, any simple statement about addiction is likely to be incomplete or even wrong. This is what makes addiction such a fascinating subject to study and a challenging problem to treat.

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Use of Psychotropic Medications During Lactation

TO THE EDITOR: With their elegant study of sertraline and desmethylsertraline levels in maternal breast milk and the serum of nursing infants, Zachary N. Stowe, M.D., and colleagues have made a major contribution to the debate over the use of psychotropic medications during lactation (1). However, although this and several smaller studies have demonstrated minuscule or unmeasurable levels of various antidepressants in breast-fed infants, there remain understandable concerns about prescribing such medications to lactating mothers. Given the important role of serotonin in the modulation of synaptogenesis in the neonatal period (2), such concerns might apply particularly to the use of selective serotonin reuptake inhibitors (SSRIs).

Most studies have concentrated on measuring the *serum levels* of antidepressants in infants, rather than their *effects*. A recent study, however, found no discernible effect of maternal sertraline treatment on the activity of the platelet serotonin transporter in four breast-fed infants (3). These represent the first data on the potential biological effects of maternal antidepressant treatment on infants.

The benefits of breast-feeding need no repeating (4), but an issue often overlooked is the risk to the infant associated with unresolved maternal depression. Children of mothers with untreated postpartum depression have reduced growth rates, delayed motor development, and lower IQs than children of mothers whose depression has been successfully treated (5, 6). In addition, we must consider the potentially devastating effects upon a child of maternal psychiatric hospitalization or suicide.

It is clear that more data are needed, particularly from longitudinal developmental studies, before we can be sure that infant exposure to SSRIs through breast milk is harmless. Nonetheless, given the enormous benefits associated with breast-feeding, the significant risks posed by untreated maternal depression, the mounting evidence that SSRIs are not found in significant quantities in infant plasma, and early data suggesting they do not produce measurable changes in infant serotonin transport, we feel that all women suffering from significant postpartum depression should be offered appropriate antidepressant treatment unless there is a clear contraindication in an individual case.

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Drs. Stowe and Owens Reply

TO THE EDITOR: We appreciate the acknowledgment of the detail provided in our earlier manuscript and share the concern raised about the unknown sequelae of infant antidepressant exposure during breast-feeding (1). The focus of the study was not to demonstrate that sertraline does or does not have an impact on nursing infants, but rather to provide some scientifically derived mechanism for minimizing infant exposure to the medication. Previous studies have reported that the milk-plasma ratio is a method of determining infant exposure (1). This method, laden with the potential confounds of aliquot of breast milk (gradient) and time after dose (time course), does not provide a method for reducing infant daily dose. Determination of the time course allows the clinician and patient to reduce infant dose of sertraline up to 24% by discarding a single breast-feeding. It also provides a medication-specific formula, currently not available for any other medication, for calculating, not estimating, the maximum infant daily dose. Defining the exposure provides the basis for future infant follow-up studies in assessing "cause and effect." Until detailed follow-up studies have been completed, we feel that every effort should be made to minimize infant exposure to medications while maintaining maternal mental health.

Epperson and colleagues made a significant contribution in assessing the potential effects of sertraline exposure in nursing infants (2). This group would have been surprised to see any effects on peripheral measures of serotonin beyond population variation with a maximum calculated infant daily dose of 0.124 mg per day of sertraline (pair 11). We are cautious about the reliability of peripheral markers to determine whether or not a medication has an effect in an infant be-

cause the possibility exists for rapid sequestering in lipophilic tissue, such as the brain, without measurable peripheral effects beyond the standard deviation. The emphasis on serotonin is warranted on the basis of the selectivity of the newer agents, yet these medications can affect other neurotransmitter systems as well. This is particularly true for the tricyclic antidepressants.

Perhaps, the terminology in the letter could be revisited, since sometimes this terminology becomes confusing in the literature about medications in breast-feeding. Terms such as "undetectable," "negligible exposure," "no significant exposure," and "harmless" are misleading, and we must remember that the infant is exposed whether or not we can detect the medication or measure an effect. We do not think that we will ever be in a position to state that a medication is "safe or harmless" in either pregnancy or lactation; this is a relative determination for each individual. Further, we think that we need to be mindful not to apply these terms—ensuring that a comprehensive risk/benefit assessment is completed on a case by case basis.

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Association Between Age at Onset of Schizophrenia and Obstetric Complications

TO THE EDITOR: Hélène Verdoux, M.D., and her colleagues (1) show a linear trend for the association of age of onset in schizophrenia and a history of obstetric complications.

In general, we agree with their conclusions and provide data supporting their results, but we were concerned with their modeling strategy. Taken seriously, it is shown that earlier age at onset of schizophrenia increases the probability of having had obstetric complications, while the real conclusion drawn is that obstetric complications decrease the probability of earlier age at onset.

To put the model in the correct order, one had to change response and explanatory variable. The difference in estimated parameters may be small, albeit they are not identical, depending on the covariance terms in the model matrix.

Further, the use of statistical techniques for meta-analysis of separate studies might result in loss of information for pooled data of individual patients. Since these data were available, one should consider using the pooled data only and including a variable indicating from which study the data came.

For our own analysis, we extracted records from the AMDP database (2) of the Department of Psychiatry, Free University of Berlin, where patient description with the AMDP system is part of mandatory clinical routine. Data from 827 schizophrenic patients (ICD-9 codes: 295.0–295.6) treated between 1981 and 1995 were eligible, i.e., information concerning age at onset of schizophrenia, obstetric complications, and affected family members was available. The sample consists of essentially unselected hospital patients. To make results comparable, we dichotomized age at onset as either 18 or 21 years, younger versus older.

Covariates were sex, a familial history of schizophrenia, and the presence of any obstetric complication. Using logistic regression, we obtained odds ratios of 1.76 (95% confidence interval: 1.03–3.02; p=0.04) for obstetric complications and of 0.61 (95% confidence interval=0.41–0.90; p=0.01) in favor of the female sex, while for familial history no significant result was found. Changing the age-at-onset criterion to 21 years and younger yielded an additional effect for familial history (odds ratio=1.68; 95% confidence interval=1.07–2.63; p=0.02) of about the same magnitude as for obstetric complications (odds ratio=1.61; 95% confidence interval=1.02–2.54; p=0.04), the effect of sex remaining about equal (odds ratio=0.54; 95% confidence interval=0.40–0.73; p< 0.001). No significant interaction terms were found.

Data originating not from planned studies, but from clinical routine will suffer from some unreliability due to unstandardized measurement. Nevertheless, we think that even if mild complications were missed, at least moderate and severe types of obstetric complications were recognized, thus explaining the somewhat higher odds ratios in our study group. Consistent with several studies, a familial history of schizophrenia also was associated with an earlier age at onset (under 22 years), although not with an age at onset under 19 years.

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Dr. Verdoux and Colleagues Reply

TO THE EDITOR: The statistical model we used was intended to explore the clinical correlates (i.e., age at onset, gender, family history) of a history of obstetric complications in schizophrenia. The model used by Schaub and colleagues addressed another question and was designed to examine the explanatory variables of age at onset in schizophrenia. The main limitation of this latter model is that it does not allow the assessment of a dose-response relationship between age at onset and a history of obstetric complications. Our model showed that the probability of having had a history of obstetric complications is diminished with an increase of age at onset. This finding was reported more simply in our conclusion as indicating that subjects with a history of obstetric complications are more likely to present with early onset schizophrenia than those without such a history. Whatever the formulation, the interpretation of this finding is similar, i.e., it demonstrates an association between age at onset and obstetric complications. We are puzzled by the second point raised by Schaub and colleagues—that information was lost in our statistical analyses—since we used precisely the method that is described in their letter. We specified that regression methods were used to obtain pooled weighted esti-

mates of the odds ratios from the individual patient data, and a variable, "study," was encoded to indicate from which study the data were obtained.

We were most interested in the findings reported by Schaub et al., which demonstrate that both family history and obstetric complications are independently associated with age at onset in schizophrenia. These results are in accordance with those of previous studies examining the relationship between family history and age at onset (1); they also confirm the association between early onset and obstetric complications. We have now examined the relationship between age at onset and the number of definite obstetric complications (categorized into a four-level variable) in the pooled sample of subjects with schizophrenia. The proportion of subjects with onset before 21 years was higher in subjects with three and more obstetric complications (68.8% of 16) than in subjects with two obstetric complications (64.0% of 25), one obstetric complication (54.5% of 101), and no obstetric complications at all (46.7% of 323). A significant linear trend was found in the association between the dependent variable, age at onset (categorized into a binary variable, <22 versus ≥22 years), and explanatory variable, the four-level variable "number of obstetric complications," in a model fitted with the variable "study" (weighted average odds ratio for linear trend=1.32; 95% confidence interval= 1.0–1.69; likelihood ratio=4.03, df=1, p=0.04). There was no evidence for heterogeneity across different studies. This result indicates that the higher the number of definite obstetric complications, the more likely the onset before 21 years. This dose-response relationship adds further evidence supporting the hypothesis that obstetric complications are involved in the pathophysiology of early-onset schizophrenia.

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Treatment of Borderline Personality Disorder

TO THE EDITOR: Congratulations to Miles S. Quaytman, M.D., and Steven S. Sharfstein, M.D. (1), for a splendidly written case report illustrating the treatment of a severely impaired patient with borderline personality disorder. It vividly portrays the affective confusion and interpersonal complexity of these often treatment-resistant patients and hints at the familial components. The patient struggles with an experience of her dependency being intolerable. This is a familiar family dynamic in such cases, in which the child's dependency is colored by negative family projections, despite the family's competence in other areas, and is then experienced by both patient and family as hateful and devouring (2). Given their experience of the child's dependency as unacceptable, the family inevitably distances her, in this case by literally putting her in the closet. These patients inevitably recreate this context in their lives and treatment settings (3).

The authors address the institutional aspects of treatment, focusing on the problem of providing a secure space for the patient to begin to integrate her disavowed, unacceptable affects and her self-destructive response to them. In the successful long-term hospital treatment, this was first attempted through seclusion and wet packs, which led to a reenactment within the treatment staff of the family's split around managing dependency. The staff learned to integrate their split, recognizing the meaning for the patient of their divisions. With this integrated interpersonal space for examined living, the patient could finally consider her own internal split about dependency. The outcome was excellent. We used to do very good work with these patients; fewer of us do now.

The question is how to construct such an interpretive environment outside of an inpatient setting. Quaytman and Sharfstein's quarter-way house seems useful, but many institutions create a continuum of care with discontinuous staffing and therapy. With every change of program, patients also experience changes in nursing and other clinical staff, doctors, treatment teams, and peer groups. It is extraordinarily difficult to build and staff competently an interpretive community where the patient can find the integration she needs without providing concomitant continuity of the psychotherapy, marital treatment, and milieu intervention. Given the patient's rapid shifts toward projection in all of these contexts, her inner and outer worlds must be worked with together—by clinicians trained in this specialized work and in communication with each other. In the hypothetical case, the crucial moment comes when the patient withdraws a negative projection from another patient. This follows her move from inpatient treatment to outpatient to quarter-way house. We wonder about the capacity of rapidly shifting settings to help patients use each other this way as well as how lasting such an internalization can be. In fact, even in the hypothetical case, there is ongoing evidence that the patient's projections simply shift into her marriage, which falls apart as she considers supervised apartment living. This follows almost a year of treatment.

In this changing treatment world, many of us have learned—as these authors have—how important it is to recognize that the responsibility for the treatment must be in the patient's hands (4). Particularly with borderline and other personality-disordered patients, it is not only possible but also essential to include resource management as part of the patient's responsibility. "Limited resources" is both a reality and a metaphor for much of these patients' experience (5, 6). Joining with patients and their families both to manage the limitations and interpret their meaning in a setting where the enactments of these issues can be grasped significantly deepens and expedites the treatment.

We support the message from Drs. Quaytman and Sharfstein. There is a great deal of learning to be derived from the excellent (although expensive) treatments of the past. We can develop new settings to maximize this learning, so that treatment-resistant borderline patients can grasp their experiences and allow themselves to have a life after treatment. This possibility requires managed care companies and their reviewers to recognize what we have learned about these patients, who are "outliers" compared with the less complicated, often first-episode, patients the behavioral health industry has in mind when it designs treatment algorithms. In the absence of this recognition, reviewers can unwittingly reenact the family system that attributes aggressive, unbearable, devouring dependency to these patients. In this repetition, these patients are at terrible risk of being thrown into the closet of chronic care.

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Drs. Sharfstein and Quaytman Reply

TO THE EDITOR: We very much appreciate the comments of Drs. Shapiro and Plakun and endorse their ideas. It is indeed difficult to construct a holding environment that provides meaningful continuity of care for severely ill patients, given the attitudes and constraints of many managed care protocols. What is just as troubling, however, is the impact of the absence of a holding environment on the clinician attempting to do this work. Without this, the clinician cannot find the financial or emotional support to deal with either his own or the patient's sense of helplessness. The therapist may begin to "identify with the aggressor" in seeing the patient as only manipulative and insatiable. Inevitably, the identity of the therapist is fragmented and diffused so that she can only see herself as a "part object" in the role of "med manager," or "treatment planner"; the doctor-patient relationship, so central to the treatment of the severely ill patient, is compromised to the extent that it, too, becomes meaningless.

We hope that more clinicians will become advocates for these patients and that enthusiasm to rediscover the importance and utility of treatment algorithms that include interpretative environments and meaning will be rekindled. These environments need not be inpatient settings; however, simply focusing on behavior or measurable goals has proven over and over to leave these patients by the wayside or labeled as chronic. Treatment that looks at these patients in depth can provide valuable research data that will help find new algorithms. As Bockoven reminds us, "It would appear that the way a society treats its mentally ill is but a manifestation or particular instance of the way the members of that society treat each other" (1). Resource allocation, we have learned, is a critical part of the patient's care and the patient must take responsibility in this arena. However, if the physician does not take responsibility to make sure that the doors to care remain open for these patients, no one else will.

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