Levetiracetam for Acute Mania

TO THE EDITOR: Levetiracetam is a novel antiepileptic drug with antikindling properties but no known mechanism that directly affects inhibitory neurotransmitters or excitatory amino acids. Although a number of newer anticonvulsants have begun to receive attention for their possible antimanic and/or antidepressant efficacy, we know of no published reports regarding these potential properties of levetiracetam. We report a patient with acute mania that stabilized with open-label levetiracetam monotherapy, recurred after drug cessation, and restabilized after drug reintroduction.

Mr. A was a 42-year-old divorced white man with a 27-year history of nonrapid-cycling bipolar I disorder. He had no psychiatric comorbidities according to the Structured Clinical Interview for DSM-IV (1) a 2–3 month history of elevated mood, pressured speech, sleeplessness, and related symptoms, and subthreshold depression (a baseline score of 25 on the Young Mania Rating Scale [2] and a score of 16 on the 31-item Hamilton Depression Rating Scale). Mr. A had experienced his first manic episode at age 15 and his first depressive episode at age 35. He had four lifetime psychiatric hospitalizations and had attempted suicide at age 39. Previous episodes had been modestly responsive to adequate trials of lithium, divalproex, carbamazepine, conventional neuroleptics, selective serotonin reuptake inhibitors, and/or psychostimulants. A 6-week trial of 1000 mg/day of divalproex and 15 mg/day of olanzapine was discontinued because of sedation and nausea, after only partial improvement of his current mania.

Levetiracetam was prescribed to Mr. A at 500 mg/day and increased by 500 mg/day over 5 weeks to 2500 mg/day. His score on the Young Mania Rating Scale decreased to 6, his score on the Hamilton depression scale decreased to 5, and he experienced no side effects. A 50% reduction in score from baseline on the Young Mania Rating Scale was seen at week 3. Euthymia was sustained for 3 weeks, until Mr. A missed 6 days of drug therapy after he missed an appointment. He was seen subsequently with reemergent mania, a score of 22 on the Young Mania Rating Scale, and a score of 22 on the Hamilton depression scale. His mania again was ameliorated after he started taking levetiracetam, 2500 mg/day. There were no further recurrences of mania by the 6-week follow-up.

Although the patient's drug discontinuation was unplanned, the swift resolution of reemergent mania after abrupt cessation was striking. The high degree of tolerability and favorable side effect profile of levetiracetam suggests it may be useful, in light of the high rates of noncompliance with many existing pharmacotherapies for bipolar disorder. Current neuropsychopharmacologic theories emphasize the importance of the upregulation of γ-aminobutyric acid (GABA) and the lowering of excitatory amino acids to explain the occurrence of mood stabilization with anticonvulsants. Newer anticonvulsants often become regarded as good candidates for mood stabilizers on the basis of these mechanisms. However, negative studies of the use of gabapentin (3) and tiagabine (4) to treat mania call into question such generalizations and suggest that additional mechanisms may be involved. The unique neuropharmacology of levetiracetam, combined with the present observations, warrant controlled studies to investigate further its possible thymoleptic properties. Pending further reports, these findings regarding one patient must be interpreted with caution.

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MECP2 Mutation in a Boy With Language Disorder and Schizophrenia

TO THE EDITOR: Rett syndrome is a severe neurodevelopmental disorder within the autism spectrum that affects females almost exclusively. It is characterized by a period of early normal development followed by regression, loss of speech and acquired motor skills, stereotypical movements, seizures, microcephaly, and disturbances of sleep (1). Most cases of the disorder are caused by mutations in the *MECP2* gene (1, 2). Few cases of affected males have been reported. One male infant died during the first year of life from congenital encephalopathy (1). Two other boys exhibited symptoms typical of Rett syndrome that were associated with a mutation of the *MECP2* gene and somatic mosaicism with the XXY karyotype, respectively (3). Mutations of the *MECP2* gene have been shown to be responsible for mental retardation in males (4) as well as in females. We report on a 12-year-old boy with developmental receptive language disorder and childhood-onset schizophrenia that were associated with a mutation of the *MECP2* gene. To our knowledge, the association of childhood-onset schizophrenia with an *MECP2* gene mutation has never been reported.

At birth Arnold weighed 3.75 kg and was 52 cm in length. The results of a pediatric examination were normal, except for a bilateral pseudomembranous syndactyly of toes two, three, and four. His psychomotor development was normal until he was 2 years of age, at which time he became irritable. At 3 years of age, he exhibited the features of developmental receptive language disorder. The initial treatment program included speech therapy, group therapy to help Arnold deal with his peers, and psychotherapy. At age 6, Arnold entered a day care program for children with developmental language disorder that included special education. Three years later, he showed dramatic improvement, although he still exhibited impaired language development.

At 12 years Arnold suddenly exhibited severe psychosis, and hospitalization was required. The results of an initial examination showed a pubertal boy with auditory and visual hallucinations, insomnia, anxiety, agitation, stereo-

typies, and delusional ideas of persecution. An EEG, a computerized tomography head scan, and the results of routine blood tests were normal. Arnold was sequentially treated with cyamemazine, pimozide, thioridazine, amisulpride, and risperidone. All drug treatments were discontinued because of adverse effects, including extrapyramidal symptoms, a cutaneous rash, a bowel obstruction, and urinary retention. His psychiatric symptoms did not seem to be influenced by neuroleptic treatment, although it caused some fluctuation in severity. After 2 months Arnold was given lithium, but it was discontinued a few days later because of vomiting. All medications were discontinued, and Arnold was transferred to a pediatric hospital unit for laboratory investigations because of his family history, a second EEG showing slow waves, and symptom fluctuation. The results of all tests, including lumbar biology, serology, cytogenetics, and a test for metabolic diseases, were normal.

Five months later, Arnold's psychotic symptoms improved. However, he was slightly hypotonic and apathetic and had lost all cognitive skills, including language. He recovered slowly during the next 6 months. One year later, he exhibited a second episode of psychosis. Low doses of chlorpromazine, 100 mg/day, improved his symptom profile. His diagnosis of childhood-onset schizophrenia, based on DSM-IV criteria, was retained. Not long ago, an alanine-140-valine mutation of the *MECP2* gene was found to exist in Arnold and his unaffected mother. Such a missense mutation (resulting in amino acid substitution), located in the methyl-CpG-binding domain of the protein, has been located in another family and was found to be associated with mild mental retardation in females and severe mental retardation in males (4).

This case report suggests that the phenotypic spectrum of mutations in the *MECP2* gene can extend beyond the traditional diagnoses of Rett syndrome and mental retardation and might include developmental language disorder and childhood-onset schizophrenia as well.

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Neuroleptic Malignant Syndrome and Quetiapine

TO THE EDITOR: Some recent reports have focused on a possible association between neuroleptic malignant syndrome and the newer antipsychotics. Two case reports (1, 2) have suggested that neuroleptic malignant syndrome may be related to treatment with quetiapine. However, the evidence is not unequivocal because of the concomitant use of other medications. We discuss a patient for whom quetiapine was almost certainly the cause of neuroleptic malignant syndrome.

Mr. A, a 28-year-old African Caribbean man, was admitted to a psychiatric clinic with a psychotic relapse accompanied by bizarre stereotypic movements, mannerisms, and profuse sweating.

Four years earlier, Mr. A had been diagnosed with schizophrenia and had been treated subsequently with haloperidol, fluphenazine, and penfluridol. Seven weeks before his present hospital admission, he had discontinued penfluridol and had started taking alprazolam, 0.5 mg b.i.d., and biperiden, 2 mg b.i.d., because of tardive dyskinesia that affected his head and upper arms. At hospital admission, this medication regimen was terminated. Quetiapine, 25 mg b.i.d., was started on the second day in the hospital and was gradually titrated to 400 mg b.i.d. by day 8. Diazepam, 10 mg b.i.d., was started on day 5 because of severe anxiety. On the seventh day, Mr. A stopped eating and drinking and developed catalepsy. He also became incontinent. On day 9 he became confused, experienced muscle rigidity, and had dry skin and mucosa. His body temperature was 102.6° F, his blood pressure was 150/100 mm Hg, and his heart rate was 120 bpm (his blood pressure at admission had been 130/90 mm Hg and his heart rate had been 88 bpm).

The results of laboratory blood tests showed a leukocyte level of 11.4×10^9/liter; his serum levels were as follows: aspartate aminotransferase: 448 U/liter, alanine aminotransferase: 126 U/liter, lactate dehydrogenase: 2288 U/liter, creatinine phosphokinase: 10,869 U/liter, creatinine: 2.34 mg/dl, urea: 77 mg/dl, sodium: 149 mmol/liter, and C-reactive protein: <0.1 mg/dl. Neuroleptic malignant syndrome was diagnosed in Mr. A, and all medication was discontinued. Mr. A was treated with ice packs, intravenous rehydration, and clonazepam, 3 mg/day. His hyperrigidity subsided within 48 hours. His temperature, pulse, and blood pressure returned to within normal ranges by the fifth day of treatment (during these 5 days, his pulse varied from 90 to 120 bpm). His laboratory measures became normal by day 10 of treatment.

An infection was ruled out as the cause of our patient's illness, as was heatstroke. The patient had not been engaged in strenuous physical activity, nor had he been exposed to high ambient temperatures. Because penfluridol had been discontinued 7 weeks before treatment with quetiapine had begun and other medications had been discontinued at admission, quetiapine was the only antipsychotic medication that was taken before the symptoms of neuroleptic malignant syndrome appeared. Furthermore, after quetiapine was discontinued, the patient's clinical symptoms subsided within several days. Therefore, we believe that quetiapine was the cause of neuroleptic malignant syndrome in this patient.

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Postpartum Panic Disorder in a New Father

TO THE EDITOR: For women, the postpartum period is a time of heightened risk for the onset or recurrence of panic disorder (1–3). However, we are aware of no published reports on the course of panic disorder in men during the postpartum period. Here is a report of a new father who had a recurrence of panic disorder after the birth of his first child.

Mr. A was a 33-year-old man who developed panic disorder with agoraphobia at age 19 and was treated with benzodiazepines by his general practitioner for several years. After enrolling in graduate school at age 27, he experienced a severe relapse into panic disorder with agoraphobia and was unable to attend his classes. He took a leave of absence while he sought psychiatric treatment. Mr. A began treatment with sertraline, 100 mg/day, and alprazolam, 0.5 mg b.i.d., and experienced a full remission of symptoms within 6 weeks. Over the course of 7 months, alprazolam was discontinued, and Mr. A remained well while taking sertraline, 100 mg/day. After 3 years of this drug regimen, Mr. A reduced his dose of sertraline to 50 mg/day and continued to stay well.

Two years later his wife gave birth to a healthy infant daughter. Although his wife was the primary caregiver for the baby, Mr. A experienced frequent nightly sleep interruptions. Within 2 weeks of the birth, Mr. A's panic disorder had recurred. The panic attacks occurred daily, and agoraphobia prevented him from leaving the house unaccompanied. He took leave from work while he sought help. A resumption of treatment with alprazolam, titrated to 0.5 mg t.i.d., and an increase in his sertraline dose, to 100 mg/day, led to substantial improvement within 2 weeks. Mr. A was able to return to work at that time. By the fourth week of treatment, he had recovered fully. Over the subsequent 4 months, he stopped taking alprazolam. Mr. A continued to be well while receiving sertraline monotherapy over the subsequent 6 months.

This report highlights the need for greater attention to men's mental health after the birth of a child. With a growing proportion of women in the workforce, men are likely to take on more child care responsibilities. Their emotional state has implications not only for themselves but also for the children in their care. Although the research literature on postpartum psychiatric disorders has grown substantially in recent years, it has focused almost entirely on women. Research on postpartum mood and anxiety disorders should be expanded to include new fathers, as should efforts to increase screening and education. This report also calls attention to the role of sleep disruptions in the course of panic disorder after childbirth. Patients with panic disorder, in contrast to patients with major depression, have been reported to experience a worsening of their condition after sleep deprivation (4).

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Increasing Insulin Dose for Olanzapine-Related Diabetes

TO THE EDITOR: Olanzapine treatment has been associated with impaired glucose metabolism, clinical diabetes mellitus, and ketoacidosis, as noted in a number of case reports (1–5). In many instances, glucose homeostasis improved or returned to normal after discontinuation of olanzapine. We found one report of ketoacidosis developing in a 12-year-old who stopped taking then restarted olanzapine; the child's glucose level then returned to normal (6). We report on a patient who never stopped taking olanzapine after developing diabetic ketoacidosis and required gradually decreasing amounts of insulin until the illness was controlled by diet.

Mr. A was a 49-year-old Caucasian man with a 22-year history of undifferentiated schizophrenia and no family history of diabetes mellitus. He was also obese. He participated in a phase III olanzapine trial at a Department of Veterans Affairs medical center. Previous treatments had included haloperidol, lithium, and trihexyphenidyl. An initial work-up revealed a random glucose level of 89 mg/dl, normal urinalysis results, and a body mass index of 34.2 kg/m^2. His history and the results of a physical examination did not suggest abnormal glucose metabolism. Mr. A's condition was maintained with olanzapine treatment, 20 mg/day, which considerably improved his symptoms.

Eleven months later, tests conducted during a scheduled follow-up visit revealed an increase in body mass index to 37.8 kg/m^2 and a 34-lb weight gain since Mr. A started taking olanzapine. He then experienced nausea, vomiting, polyuria, and polydipsia and went to the emergency room, where a serum glucose level of 766 mg/dl was detected. Mr. A left the hospital against medical advice and without treatment; he returned 8 days later. The results of a work-up at the time showed a serum glucose level of 368 mg/dl, a urinalysis with 4+ ketones and 4+ glucose, a pH of 7.10, and an anion gap of 29.0. He spent a day in the intensive care unit with ketoacidosis, received intravenous fluids and insulin, was transferred to a medical unit, and was ultimately discharged while receiving 94 U of regular and neutral protamine Hagedorn insulin per day.

After we obtained several low-normal serum glucose levels, we decreased his daily insulin dose to 78 U. His insulin requirement continued to decrease until he required no further medication for control of glucose levels. Since he started taking olanzapine, his body mass index has fluctuated between 34.2 and 37.8 kg/m^2; his hemoglobin

HbAlc levels have been measured at between 5.4% and 6.5%. Mr. A's serum glucose levels in the last year have ranged from 112 to 164 mg/dl. His latest serum insulin level was 56.3 μU/ml (normal range=0–30), and his C-peptide level was 10.7 ng/ml (normal range=0.9–4.0). Mr. A continues to take his initial olanzapine dose of 20 mg/day and has experienced no new medical or psychiatric sequelae. He has never been treated with oral hypoglycemics and has subsequently been hospitalized only once, for psychosocial stabilization.

It was unclear to the investigators in the phase III study whether olanzapine could precipitate ketoacidosis. The dramatic improvement in the patient's schizophrenia symptoms was noted by the patient and his family. This, along with the as-yet-unreported association of the drug with diabetes mellitus, made the risk-benefit factors weighted toward continuing olanzapine treatment. Weight gain, serotonin 5-HT_{1A} and 5-$HT_{2A/C}$ receptor antagonism, insulin resistance, and elevated insulin, leptin, and serum lipid levels have all been implicated in this phenomenon (7). Although Mr. A's prediabetic insulin and C-peptide levels were not available, this report suggests that olanzapine may have triggered a biphasic reaction, initially causing suppression of insulin secretion then subsequent rebound overcompensation. This also suggests possible future depletion of beta cells and a return to an insulin-dependent state. Further study of this phenomenon, including the role of peripheral insulin receptors, is warranted.

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Female Psychiatrists

TO THE EDITOR: I greatly enjoyed reading the article by Erica Frank, M.D., M.P.H., and colleagues about female psychiatrists (1). However, I was amazed that the authors made so little of the fact that female psychiatrists are almost twice as likely as other female physicians to be the main caregivers of preschool children. They neglected to investigate whether the perceived high stress level of their study group could be attributed largely to this factor (although the physicians interviewed were discussing work-related stress). Zachary Stowe, M.D., of Emory University pointed out in a grand rounds at California Pacific Medical Center several years ago that the demographic group most likely to experience depression is mothers of children age 4 and younger. Personally speaking, I found that the years when I struggled to work, run the household, and care for my toddler and preschooler without much domestic help were as stressful as internship and far more stressful than residency (in which I "worked" two to three times as many hours but got a lot more sleep). I am very grateful for the opportunity I had to be with my children when they were young and feel melancholy as my younger child gets ready for kindergarten. However, I also notice my stress level dropping and the enjoyment of my work increasing. It would be interesting if the authors could go back and look specifically at the experience of those mothers.

In fact, the authors' study provides a wonderful opportunity to look at how female physicians attempt to combine the commitments of motherhood and medicine. In fact, there is all too little discussion about how to do both. Parents who do not spend the majority of their time with their small children have no idea of the balancing act and regrets that go into each decision about allocation of their time. I think it is true that many female doctors who want to raise their children choose psychiatry for the flexibility and time boundaries that it offers and because it still allows for a rich and exciting professional life. I would also be interested in hearing about the cohort of psychiatrists in the study after 8 years, when their preschoolers are older and more independent. I would not be surprised to learn that the group has become more accepting of professional burdens, is working longer hours, and is feeling less stressed.

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Dr. Frank and Colleagues Reply

TO THE EDITOR: We thank Dr. Burke for her comments about our article and welcome the opportunity to expand on our analysis of the interaction between psychiatrists' work and home lives. Unfortunately, the cross-sectional nature of our study may have misled Dr. Burke into thinking that there were associations between psychiatrists' current stress levels and their having ever been their child's primary preschool caretaker (regardless of the child's current age).

Unfortunately, our study group included only 32 married psychiatrists, now aged 30–40, who recorded their child care arrangements and had children who are now 6 years old or younger. Only six of these psychiatrists reported being their children's primary preschool caretaker. The size of this group, of course, precludes meaningful analysis. When we looked at stress and career satisfaction of all female physicians aged 30–

40 who now have children age 6 or younger, stratified by whether or not they are/were their children's primary preschool caretaker, we found the following. Among married female physicians in which the woman was the primary caregiver (N≥80), 7% had high levels of home stress, 11% had high levels of work stress, and 46% were always or almost always satisfied with their careers. Among women with similar characteristics who were not their children's primary caregiver (N≥536), 9% had high levels of home stress, 11% had high levels of work stress, and 46% were always or almost always satisfied with their careers. The differences between the groups were nonsignificant. Among all married women physicians aged 30–40 with a child 6 years or younger (N=633), 8% had high levels of home stress, 11% had high levels of work stress, and 46% were always or almost always satisfied with their careers. Among similar women physicians without a child age 6 or younger (N=75), 11% had high levels of home stress, 15% had high levels of work stress, and 38% were always or almost always satisfied with their careers. The differences between the groups were nonsignificant.

Discussions of "physician stress" are always popular in the literature. However, these data suggest that home stress, work stress, and career satisfaction were not adversely affected either by having children or by being their primary caretaker during their younger years. Further, we previously reported (1) that among postmenopausal female physicians, those who had had more children reported more current career satisfaction (test for trend, $p<0.001$). Most parents can neither afford the domestic help to which Dr. Burke alludes nor work part-time and still command relatively high wages. It seems that female physicians' access to multiple professional and personal options has unsurprisingly positive consequences.

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Discipline for Psychiatrists

TO THE EDITOR: James Morrison, M.D., and Theodore Morrison, M.P.H. (1), concluded in their article that psychiatrists were significantly more likely than nonpsychiatric physicians to be disciplined for sexual relationships with patients. However, in reaching a conclusion with possible widespread implications, the authors did not present the data typically seen in other published scientific studies. Specifically, the definition of "sexual contact" used by the board was not reported. The process used to determine whether "sexual contact" occurred was also not defined.

The authors acknowledged that the psychiatrist's office is a unique medical setting involving, for example, isolation from other professionals. However, it is unclear to what extent psychiatrists, compared to nonpsychiatric physicians, made judgments regarding sexual misconduct in these cases. Similarly, the background of the psychiatrists involved, specifically their type and level of expertise in dealing with such issues, was not discussed. Also, whether the medical board sought consultation with the state psychiatric association to validate its findings was not mentioned.

Without this information, the article can be seen as suggesting another unsettling hypothesis that the authors did not consider. Psychiatric patients may be more apt to file questionable or distorted complaints with a state board, and at least a subgroup of psychiatrists may seek to settle when confronted with an expensive adversarial process in an unfavorable environment.

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Drs. Morrison and Morrison Reply

TO THE EDITOR: The Medical Board of California defines "sexual contact" as "sexual intercourse or touching of an intimate part of a patient for purpose of sexual arousal, gratification, or abuse." However, that is not quite the point, inasmuch as we used the term only in our discussion (and abstract) as shorthand for "sexual relationships or other inappropriate personal contact with patients." These matters are basic biology; nearly all incidents involve body violations that any person on the street, let alone any psychiatrist, would agree are out of bounds.

The process used to determine whether a sexual relationship has occurred is through a thorough investigation that includes interviews with the complainant, the physician, and all other persons who might have relevant information. If validating factual information is lacking, the state psychiatric association is not involved in this process. When an allegation goes to investigation, it is with input from a board-certified psychiatrist who must have recent active practical experience and have no disciplinary actions completed or pending against him or her.

Board officials explain that they do not operate in an environment that is unfavorable to physicians. There is a presumption of innocence until the facts are established to a degree that is "clear and convincing to a reasonable certainty." Certainly, the public records of these investigations leave the reader in no doubt as to the appropriateness of the actions taken. No accusation is taken on faith, and no action is taken on the basis of an uncorroborated complaint. Although the Medical Board of California does not keep such data, its investigators report that spurious accusations against psychiatrists appear to be no more frequent than for other physicians.

We believe that prevention can be achieved through education and reeducation, which requires continuously keeping the problem on the radar screens of all mental health providers. To that end, we thank Dr. Burstein for his comment. In their anxiety to protect the innocent, we hope that mental health professionals will neither blame the victims nor ignore the signs that a clinician has become lost in the dark conti-

nent of desire. In either event, we find ourselves camping at the headwaters of denial.

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Treatment of Psychosis at Onset

TO THE EDITOR: In a recent editorial, Jeffrey A. Lieberman, M.D., and Wayne S. Fenton, M.D. (1), noted that an untreated first episode of psychosis constitutes a major mental health problem and advocated early detection and treatment. There may be several reasons why untreated psychosis is an important public health problem, but the evidence for some of the reasons is debatable. One reason for early detection and intervention, however, raises no questions and is obvious to anyone who has been touched by the illness. Drs. Lieberman and Fenton stated it succinctly: "Untreated psychosis damages lives" (p. 1728).

This "collateral damage" can be extensive and, as Drs. Lieberman and Fenton described, can impose "a significant burden of terror, suffering, and bewilderment on patients and their families" (p. 1728). Specifically, impairments in functioning can disrupt adolescent and young adult development at a crucial and already complex stage of life. Other potentially associated problems involve stigma, embarrassment, isolation, loss of mastery and control, diminution of self-worth, a disrupted educational and/or professional trajectory, a wounded capacity for therapeutic alliance, and a hindered capacity to participate fully in treatment decisions. Research can be very useful in delineating specific ways in which collateral damage evolves and how delays in identification and treatment occur.

Early identification and treatment may reduce this damage. A method that offers the opportunity to treat psychosis immediately at onset is one in which patients are identified in a putatively prodromal phase of the illness and either followed prospectively or enrolled in a clinical treatment or prevention trial. Patients in the Prevention Through Risk Identification Management and Education (PRIME) Research Clinic in New Haven, Conn., are actively symptomatic and have been identified as being at imminent risk for developing schizophrenic psychosis. We monitor them closely and then treat them with antipsychotic medication immediately upon onset of symptoms if they reach psychotic levels of intensity. Thus far 11 patients have converted from a prodromal to a psychotic state and have received treatment at onset.

No patients have required hospitalization as a result of having developed psychosis. All but one continued with intended daily activities of work or school (days absent: mean=0.17, SD=1.12), as well as with long-term plans (e.g., remaining in school, entering college, or maintaining their position in the job hierarchy). All of the patients maintained strong ties and good relationships with their members of their immediate family and sustained their social networks. Overall medication compliance, as measured by mean pill count, was 93% (SD=10), and seven of nine patients have thus far completed treatment.

We are aware that early identification of illness in the prodromal phase is associated with a risk of labeling and possibly stigmatizing patients and can have negative consequences for their social networks and self-esteem. Our experience, however, suggests that this approach may prevent a powerful source of stigma, i.e., untreated and undetected irrational behavior and hospitalization. Our data are clearly anecdotal, and our group was very small, but our clinical experience is compelling enough to share and suggests that preventing collateral damage through early detection and prevention should be an area of active investigation.

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Action of Atypical Antipsychotics

TO THE EDITOR: Shitij Kapur, M.D., Ph.D., F.R.C.P.C., and Philip Seeman, M.D., Ph.D., F.R.S.(C.), seemed to suggest in their article (1) that antipsychotic drugs that have atypical properties have more rapid rates of dissociation from dopamine D_2 receptors than those with typical properties. However, this conclusion is incompatible with their own report (2) that sertindole, which most certainly is an atypical antipsychotic drug because of its very low propensity to cause extrapyramidal symptoms, has the same k_{off} as haloperidol, the prototypical typical neuroleptic drug. Despite this clear failure, their theory might have had credibility if they had offered as proof even one atypical antipsychotic drug that had been developed on the basis of this theory. To my knowledge, they have not done so. By contrast, risperidone, olanzapine, quetiapine, ziprasidone, and iloperidone, all clearly atypical antipsychotic drugs, were explicitly selected for clinical development on the basis of the "serotonin 5-HT_{2A}/D_2 hypothesis"that Drs. Kapur and Seeman reject and were then shown to be atypical antipsychotics in both basic research models and clinical studies. In addition to the atypical antipsychotic drugs mentioned, there are at least a half dozen other agents of diverse chemical classes selected on the basis of the 5-HT_{2A}/D_2 hypothesis during their early development. Most people engaged in drug development agree that a valid theory should be capable of generating new chemical entities.

It has been shown clearly by my colleagues and me (3) and by others (4) that the combination of 5-HT_{2A} and D_2 receptor blockade has an important influence on the release of dopamine in the limbic system, striatum, and cortex. The effect of dopamine release in the limbic system is important for the antipsychotic activity of these compounds, while the effect in the striatum is important for the drugs' low level of extrapyramidal symptoms. The drugs' effect in the cortex is likely to be relevant to their ability to improve cognition and negative symptoms and, perhaps indirectly, their antipsychotic effect as well by means of cortical control of subcortical dopamine release. Given the emphasis by Drs. Kapur and Seeman on the importance of their theory regarding the release of endogenous dopamine in displacing antipsychotic drugs from dopamine receptors, it is extremely difficult to understand how they could reject one of the most important determinants of

the release of dopamine in the terminal regions of the limbic system, striatum, and cortex as being important to the actions of atypical antipsychotic drugs. Indeed, at one point, Drs. Kapur and Remington (5) strongly supported the importance of 5-HT receptor antagonism in the atypicality of clozapine and related compounds.

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TO THE EDITOR: Drs. Kapur and Seeman proposed an interesting hypothesis that fast dissociation from D_2 receptors explains the action of atypical antipsychotic agents. I propose that the lower affinity—the lower ratio of k_{on} (association rate constant) to k_{off} (dissociation rate constant)—of D_2 receptors explains the action of atypical antipsychotics. I will discuss this hypothesis on molecular and systemic levels, as the authors did.

The authors' hypothesis derives from two intriguing experimental findings at the molecular level. First, differences in the affinity of antipsychotic agents for D_2 receptors are driven by differences between their k_{off}, not between their k_{on}. Second, atypical antipsychotic agents have much higher k_{off} (fast k_{off}) at D_2 receptors than do typical antipsychotic agents. On the basis of these findings, the authors hypothesized that the action of atypical antipsychotic agents may derive from faster dissociation from D_2 receptors and explained that "when the concentration of endogenous dopamine rises in response to physiological stimuli, drugs like clozapine (which have a nearly 100 times faster k_{off} [than haloperidol]) decrease their occupancy much faster and provide much more access to surges of dopamine" (p. 364). According to receptor binding kinetics, antipsychotic agents and endogenous dopamine compete with each other to occupy D_2 receptors because of their affinities for D_2 receptors. Since the affinity of an antipsychotic agent is determined by the ratio of k_{on} to k_{off}, the degree of unoccupied receptor accessible to endogenous dopamine is determined not only by how quickly the drugs dissociate from D_2 receptors but also by how slowly the drugs associate to D_2 receptors. Thus, antipsychotic agents with slower k_{on} can provide more access to surges of dopamine, as antipsychotic agents with faster k_{off} do. Although the atypical antipsychotic agents that the authors have tested so far showed faster k_{off}, it is always possible that newer atypical antipsychotic agents have low affinity and slower k_{on}, rather than faster k_{off}. Thus, faster k_{off} is not the exclusive criterion for the atypical action of antipsychotic agents, but the lower affinity and faster k_{off} and/or slower k_{on} are the criteria for the atypical action of antipsychotic agents.

At the systemic level, the authors proposed that the much more transient occupancy of the D_2 receptors by atypical antipsychotic agents is associated with transient prolactin elevation and fewer extrapyramidal side effects (1). The authors claimed that this transient effect is accounted for by faster k_{off}. However, the transient occupancy of D_2 receptors by single doses of atypical agents may not exactly reflect the pattern of D_2 receptor occupancy when patients reach a plateau after multiple doses of the drugs, by which time D_2 receptor occupancy would be greatly prolonged. Another potential problem with the theory for the transient occupancy of D_2 receptors by atypical antipsychotic agents is its relationship with the onset of clinical response. A large body of evidence indicates that dopamine cell activity is dramatically reduced and that, subsequently, release of endogenous dopamine is greatly reduced within 2–3 weeks of drug administration (2). Clinical response is usually shown within 2–3 weeks of the administration of antipsychotic agents. At this time, atypical antipsychotic agents may occupy D_2 receptors much more because the synaptic concentration of dopamine is greatly reduced. Thus, D_2 receptor occupancy by the atypicals at or after this point in time may be more relevant to the drugs' antipsychotic action.

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Drs. Kapur and Seeman Reply

TO THE EDITOR: We thank Drs. Meltzer and Shim for their thoughtful comments. Dr. Meltzer raises a valid issue that sertindole's k_{off} is rather close to the range for typical antipsychotics, although the drug is an atypical antipsychotic. This is a valid concern; however, it is not just the k_{off} of the drug, but also its in vivo occupancy range, that is critical for atypicality. In that regard, sertindole at 8–24 mg/day occupies 61%–72% of D_2 receptors (1, 2), which should give rise to response without extrapyramidal symptoms. Further, a patient taking sertindole, 20 mg/day, who had also received 100 mg of fluphenazine decanoate 52 days before brain imaging had 86% D_2 occupancy. This patient exhibited akathisia (2), despite the fact that the patient would have had high 5-HT_2 occupancy.

We do not suggest that 5-HT_2 receptors make no contribution to the overall picture of atypicality. We propose that 5-HT_2 receptors are not necessary for atypicality, as shown by studies of amisulpride, remoxipride, and now aripiprazole, and that they are not sufficient for atypicality, as shown by

studies of MDL-100907 and fananserin. Even in drugs with mixed 5-HT_2 and D_2 action, D_2 receptor affinity is the biggest factor for atypicality. In fact, Meltzer et al. (3) stated, "The *low D_2 affinity* values of atypical drugs contribute more than their *high 5-HT_2 affinity values*" (emphasis added); 64% of the typical-atypical difference, as revealed by discriminate function analysis, was accounted for by low affinity at the D_2 receptor, and only 17% was accounted for by the addition of 5-HT_2 receptor affinity (3).

Dr. Shim questions whether a slow k_{on} and low affinity could also give rise to atypicality. The affinity of a drug is the ratio k_{off}/k_{on} (not k_{on}/k_{off}, as Dr. Shim suggests) (4). While current differences among atypical antipsychotics are driven mainly by k_{off}, it is possible in theory that if k_{off} were held constant, there could exist a low-affinity drug by virtue of a very slow k_{on}. However, it is important to understand that k_{on} and k_{off} are rate constants (not the rates of association and dissociation). The rate of association is a function of k_{on} multiplied by the concentration, whereas the rate of dissociation depends on k_{off} alone. Since low-affinity drugs are given at much higher doses than high-affinity drugs, even if the k_{on} (the association rate constant) were low, the rate of association would still be high because of the high concentration. This is why we think that low affinity and fast k_{off}, and not low affinity and slow k_{on}, is important to atypicality.

Thus, "atypicality" should be seen as a continuum rather than as a dichotomy. Antipsychotics become increasingly more atypical (i.e., have less chance of extrapyramidal symptoms) as their affinity at the D_2 receptor decreases and their k_{off} increases. We are not suggesting that antipsychotics with no D_2 affinity are not possible, only that there are none at present.

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Fluoxetine and Olanzapine for Resistant Depression

TO THE EDITOR: I read the article by Richard C. Shelton, M.D., et al. (1), which reported the superior efficacy of olanzapine plus fluoxetine for treating resistant nonpsychotic unipolar depression compared with either agent alone. The investigation had two main phases: a 6-week open-label trial of fluoxetine, followed by an 8-week double-blind trial in which nonresponders to fluoxetine alone were randomly assigned to receive olanzapine alone, fluoxetine alone, or fluoxetine plus olanzapine. Patients in the group receiving olanzapine alone stopped taking fluoxetine on the day of random assignment. After 1 week of treatment, fluoxetine plus olanzapine produced a marked improvement in depression symptoms, significantly much greater than that seen with olanzapine alone and with fluoxetine alone. The marked improvement persisted during the remainder of the 8-week double-blind trial and during the following 8-week open-label extension period. This interesting finding seems to me difficult to understand, because the group receiving olanzapine alone had stopped taking fluoxetine on the day of random assignment. Because fluoxetine and its active metabolite, norfluoxetine, take many weeks to disappear from the bloodstream after discontinuation (2), the group receiving olanzapine alone continued to have significant plasma levels of fluoxetine, at least during the first weeks of the double-blind trial. Therefore, the observed marked difference in response to olanzapine alone compared with the response to olanzapine plus fluoxetine during the double-blind trial seems difficult to understand because the treatments were similar.

Furthermore, the small groups (N=10, 8, and 10) examined may have led to a significant difference among the groups that was caused by chance alone (3). Replication in much larger groups by using a selective serotonin reuptake inhibitor with a short half-life could produce clearer results.

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Dr. Shelton Replies

TO THE EDITOR: The observation noted by Dr. Benazzi is indeed puzzling: Why should the beneficial effect demonstrated in the group receiving continuation fluoxetine plus olanzapine not be seen in the group receiving olanzapine and placebo? The rationale is that since fluoxetine had been recently discontinued in the latter group, sustained plasma levels of fluoxetine and norfluoxetine would have been expected because of the long half-life of the two compounds. The point made by Dr. Benazzi that the differences could have occurred by chance clearly is a possibility, and we agree strongly that a larger clinical trial is needed to establish any treatment effect. However, are there other possible explanations? After discontinuation, the plasma levels of fluoxetine and norfluoxetine would have begun to decline progressively and might have fallen below the critical threshold required to produce the effect. However, a transient effect in the olanzapine group is suggested by the response seen in the group receiving olanzapine and placebo in the third week of treatment (Figure 1). Or the combination effect could be a result of a heretofore un-

known mechanism of action. Clearly, more research is needed to test the effectiveness of this combination and any possible pharmacological effects of treatment.

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Personality Change After Treatment

TO THE EDITOR: I would like to provide some background from the literature for the report by David J. Hellerstein, M.D., et al. (1). Although the authors' finding appears to be solid and valid, it is not new. There is literature going back decades regarding how treatment of an axis I disorder can reduce measured personality dysfunction in both anxiety and depression (2–4). There is also literature indicating that these personality changes have clinical significance (5). Finally, there is also a growing literature on the effects of pharmacology on personality; an example is a review by Soloff (6).

A review of the literature shows the discussion moving forward from replicated findings to the meanings of the findings themselves. There is the question of whether the findings are measurement artifacts, treatment responses secondary to the treatment of an axis I disorder, or responses secondary to direct treatment of personality symptoms themselves. These are the more interesting questions. There was an empirical report (7) containing the suggestion that there may be an entity called a "stress-induced personality disorder," which, under the stress of an axis I illness, appears similar to a personality disorder but remits with the treatment of the axis I disorder. I applaud Dr. Hellerstein et al. for moving this topic into a useful area of research. I hope they find the previous literature helpful in their future endeavors.

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Dr. Hellerstein and Colleagues Reply

TO THE EDITOR: Dr. Reich raises useful points in his letter, in particular by drawing attention to the extensive prior research on the interrelationship between axis I disorders, such as depression and panic disorder, and personality dysfunction. As Dr. Reich points out, over a decade of studies have described a number of ways in which such factors interact.

However, we believe our article is not merely a restatement of existing knowledge; several aspects are noteworthy. First, we reported on a large population of dysthymic patients, more than 400 individuals whose low-grade chronic depression had an average duration of over 30 years. The temperamental abnormalities noted in these subjects at baseline with Cloninger's Tridimensional Personality Questionnaire (1) (including harm avoidance scores that were nearly two standard deviations above community norms) were comparable to those of more severely symptomatic individuals with disorders such as major depression. Second, our study demonstrated that for our dysthymic subjects, elevated levels of harm avoidance correlated with poor social functioning (as measured with the Social Adjustment Scale) at r=0.50 at both pre- and posttreatment, which implied that temperamental variables may be an important component of these patients' social dysfunction. Third, to our knowledge, our report is the first large study of dysthymic patients to assess the impact of selective serotonin reuptake inhibitors on temperament and has the advantage of comparison groups receiving placebo or a tricyclic antidepressant.

Dr. Reich's conceptualization of a "stress-induced personality disorder" resulting from anxiety or mood disorders is one possible explanation for the temperamental abnormalities that have been noted in a variety of such patients. It is also possible that preexisting abnormalities could be a substrate on which such axis I disorders later develop. Prospective studies following large groups of subjects from childhood through adulthood are needed to clarify the sequence in which such disorders appear and to elucidate causative factors.

Finally, we feel that our study raised the provocative issue of treating temperamental abnormalities. Dr. Reich refers to Soloff's summary of pharmacological options in the treatment of personality disorders (1998). There is indeed a growing literature on drug treatment for borderline and other personality disorders. There is less research on the treatment of temperamental abnormalities such as we observed. In groups of patients with chronic and trait-like disorders such as dysthymic disorder and generalized anxiety disorder, future treatments may be targeted not only at symptom remission but at normalization of coexisting temperamental distortions.

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Abuse and ACTH Response to Corticotropin-Releasing Factor

TO THE EDITOR: The article by Christine Heim, Ph.D., et al. (1) contains a misinterpretation concerning an article by my colleagues and me (2) that I would like to address. The article by Dr. Heim et al. showed that abused women without major depressive disorder exhibited greater than usual ACTH responses to corticotropin-releasing factor (CRF) administration, whereas abused women with major depressive disorder and depressed women without early life stress showed blunted ACTH response to ovine CRF administration (1). In our study, we showed that sexually abused girls recruited from a longitudinal prospective study demonstrated blunted ACTH response to ovine CRF. The article by Dr. Heim et al. incorrectly stated that "PTSD [posttraumatic stress disorder] was not systemically evaluated and the abused girls were not subgrouped according to the presence or absence of psychiatric disorders" (2, p. 579). In our article (2, p. 250), we stated that the subjects were evaluated with the Diagnostic Interview Schedule for Children and Adolescents (Washington University, St. Louis) to obtain DSM-III-R psychiatric diagnoses. The Diagnostic Interview Schedule for Children and Adults includes an evaluation for PTSD. In our Results section (p. 251), we also stated that there were "no significant effects of the presence of histories of dysthymia or of suicide attempt(s)" on plasma ACTH response to ovine CRF in the abused group.

Thus, our findings regarding sexually abused girls were similar to those of Dr. Heim et al. regarding depressed women who had histories of adverse life events. Correction of this misinterpretation may influence the discussion of their findings.

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TO THE EDITOR: Dr. Heim et al. reported that adult survivors of childhood abuse may have altered pituitary-adrenal axis response to provocative challenge tests. These authors found that nondepressed, formerly abused women exhibited a significantly greater ACTH response to CRF stimulation than comparison women, but it seems possible that the differences observed might be entirely due to differences in the ethnic composition of the study groups.

Specifically, as Dr. Heim and colleagues correctly noted, African American individuals showed about twice as much ACTH response to CRF administration as Caucasians. If we assume that the nonwhite subjects in this Atlanta-based study were all African American, then 55% of the abused women without depression were African American, as opposed to only 25% of the comparison women and 15% of the women in the two depressed groups. These ethnic ratios could therefore account almost perfectly for the differences in ACTH response shown in the authors' Figure 1 without reflecting any effect of depression or history of abuse. The authors themselves noted that there was a highly significant race-by-time interaction in their analyses. Therefore, I think the authors would have been obliged to report the results separately by race (and perhaps by education) since Dunn's multiple comparison procedure might not have been sufficient for analysis in this instance. It would be helpful if the authors would clarify this issue and, in particular, provide summary data for findings among the various groups broken down by race (and perhaps by education).

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Dr. Heim and Colleagues Reply

TO THE EDITOR: One of the major strengths of our recent study on pituitary-adrenal responses to standard pharmacological challenge tests in adult women with a history of childhood abuse was a balanced study design regarding the four groups of abused or nonabused women with or without major depression. Indeed, we demonstrated that ACTH responses to ovine CRF differed markedly between abused women with concurrent major depression and abused women without concurrent major depression. These findings demonstrated that it is imperative to control for concurrent symptoms of psychopathology when studying neuroendocrine function in victims of childhood abuse. According to our reading of the study by Dr. De Bellis et al. (1994), structured interviews for the diagnosis of psychiatric disorders in sexually abused girls had been performed at some point during a longitudinal study. However, it was not clear that current psychiatric symptoms (except for symptoms of depression) were systematically evaluated at the time of the neuroendocrine investigation. Accordingly, the authors subdivided abused girls on the basis of a history of dysthymia and not on the basis of concurrent symptoms or diagnoses. We showed that concurrent, but not past, symptoms or diagnoses of depression affected pituitary reactivity to CRF administration. In addition, Dr. De Bellis et al. did not report findings on the prevalence of PTSD and the effects of PTSD on neuroendocrine responses throughout their article, although 20%–70% of sexually abused children reportedly suffer from PTSD (1).

With respect to the effects of race on our findings, we point out that the analyses of variance (ANOVAs) of the effects of history of childhood abuse and current major depression on hormone profiles throughout the challenges were corrected for the effects of race by introduction of this variable as a covariate. Dunn's multiple comparison procedures were also adjusted by using pooled mean square errors derived from analyses of covariance. In accordance with the literature (2), we found that race affected ACTH concentrations in the CRF stimulation test. When controlling for the influence of race, we found significant three-way interaction effects of childhood abuse, major depression, and time in all analyses. It is noteworthy that in contrast to our study, previous studies assessing the effects of race on pituitary-adrenal reactivity to challenges did not control for histories of early life stress (2, 3), which may have affected these findings. We considered introducing race as an independent factor in the ANOVAs, re-

sulting in means for different races within the study groups; however, the small number of nonwhite subjects in three of the four groups did not allow for meaningful results. When limiting the group comparisons to white subjects, we were able to support our previous findings (data not shown). We acknowledge that race markedly affects pituitary reactivity and extend Dr. Merskey's comment by suggesting that race may represent a constitutional factor that interacts with early environmental influences in shaping a phenotype with vulnerability to stress and disease. The role of race in the neurobiology of early-life stress deserves further attention in future studies.

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