## Rhabdomyolysis, Pancreatitis, and Hyperglycemia With Ziprasidone

TO THE EDITOR: Atypical antipsychotics have been associated with neuroleptic malignant syndrome, rhabdomyolysis, pancreatitis, and type 2 diabetes mellitus (1–3). We describe what we believe to be the first report of these complications attributed to the newer atypical antipsychotic agent ziprasidone. This case was reported to the Food and Drug Administration's MedWatch.

**Ms. A, a middle-aged woman with schizoaffective disorder, had been treated for many years with clozapine, risperidone, and lithium. She had no history of diabetes mellitus, renal disease, pancreatitis, or substance abuse. Two weeks before admission, her risperidone therapy was discontinued, and ziprasidone treatment, 40 mg/day, was initiated. Ms. A was admitted for an altered mental status with a decreased level of consciousness, agitation, and disorientation. Her body temperature was 38.5°C (her maximum temperature was 41.3°C on hospital day 3), her blood pressure was 160/100 mm Hg, and her pulse was 112 bpm. She had no muscle rigidity at admission or during her hospital course.**

**Results of a physical examination were otherwise unremarkable. Results of laboratory studies included a negative toxicology screen and alcohol level; a low lithium level; an elevated WBC count (15,000 cells/μl); negative urine, blood, and CSF cultures; an elevated creatinine level (1.8 mg/dl, which peaked at more than 7 mg/dl on hospital day 7); an elevated glucose level (250 mg/dl, which increased to 980 mg/dl a day later); a creatinine kinase level of more than 64,000 U/liter during the first week in the hospital; and a sevenfold increase in pancreatic amylase with pancreatic inflammation found on an abdominal computerized tomography scan.**

**Ms. A's ziprasidone and lithium treatments were discontinued. Clozapine was initially discontinued but was later restarted for severe psychosis. Ms. A's mental status returned to its baseline level, and her pancreatitis resolved. Hemodialysis was required for 1 week, after which renal function gradually returned. Severe hyperglycemia without ketoacidosis was managed with intravenous insulin, initially requiring up to 200 units over 24 hours. Over 3 weeks the hyperglycemia gradually improved until diabetes medication was no longer required.**

The patient's rhabdomyolysis, hypertension, and fever associated with the initiation of ziprasidone treatment suggest neuroleptic malignant syndrome, although the patient never had muscle rigidity. An absence of muscle rigidity with neuroleptic malignant syndrome has been reported (4, 5). This case illustrates the possibility of adverse reactions to ziprasidone, which are similar to those associated with other atypical neuroleptics.

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## Ziprasidone and Migraine Headache

TO THE EDITOR: The side effect of weight gain with atypical antipsychotics has drawn much attention to ziprasidone over the past year. Many of the patients in our county mental health system have developed serious health problems associated with obesity, not to mention a negative self-image, while taking the older atypical antipsychotics. In switching obese patients to ziprasidone, we have gained some ground with the weight issue, found comparable efficacy (clozapine excepted), and, in one case, encountered side effects as unique as ziprasidone's receptor antagonist profile.

**Ms. A, a 41-year-old obese African American woman with a diagnosis of schizoaffective disorder, had been treated with risperidone and fluoxetine for 5 years. Ms. A had been switched recently from fluoxetine to citalopram secondary to "fluoxetine poop-out." Her depression persisted, yet it soon remitted when I increased her citalopram dose to 40 mg/day. Her psychotic symptoms were more stubborn.**

**Although she had improved dramatically when switched from trifluoperazine to risperidone earlier, she continued to experience paranoia and low-grade auditory hallucinations along with negative symptoms, such as social isolation and poor initiative. Attempts to optimize treatment with risperidone were thwarted by side effects at higher doses. Ms. A struggled along taking risperidone, 8 mg/day, plus benztropine for extrapyramidal symptoms. She weighed 225 lb and had hypertension and type 2 diabetes mellitus. By cross-titration her antipsychotic was switched to ziprasidone, reaching a goal oral dose of 80 mg b.i.d. Risperidone and benztropine were discontinued without incident or regret.**

**At her follow-up, Ms. A had lost 9 lb and was no longer experiencing auditory hallucinations or paranoia. She had, however, developed acute trismus and photophobia, which were both painful and distressing. She reported no headaches and had no history of migraine. Her ziprasidone treatment was lowered to an oral dose of 60 mg b.i.d.; oral clonazepam, 0.5 mg at bedtime, was added. At her follow-up a week later, the trismus and photophobia had resolved. Further improvement in Ms. A's negative symptoms was also noted. Her positive symptoms remained in remission.**

In vitro studies of ziprasidone (1) have revealed strong antagonism at the serotonin 5-$HT_{1D}$ receptor, the target of the triptan line of 5-$HT_{1D}$ agonist antimigraine drugs. Although Ms. A was not a migraineur, nor did she use a triptan, her development of photophobia suggests the possibility of a duel at the 5-$HT_{1D}$ receptor. I encourage any physician treating a patient with both ziprasidone and a triptan to assess the patient for diminished triptan efficacy. Since ziprasidone is such a clinical newcomer, any case reports of such a drug-drug interaction would be helpful.

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## Tardive Dyskinesia and Ziprasidone

TO THE EDITOR: Cases of tardive dyskinesia associated with atypical neuroleptic medications have been reported (1); however, we are not aware of any cases in which tardive dyskinesia has been associated with ziprasidone. Ziprasidone, a newer atypical neuroleptic, is a serotonin 5-$HT_{2A}$, dopamine $D_2$, and $\alpha_1$ inhibitor, with a greater affinity for the 5-$HT_{2A}$ receptors than for the $D_2$ receptors. It is a benzothiazolylpiperazine, structurally dissimilar to other antipsychotics, and is the only atypical antipsychotic that is an agonist at 5-$HT_{1A}$ receptor sites, an antagonist at 5-$HT_{1D}$ receptor sites, and an inhibitor of both norepinephrine and serotonin reuptake. Ziprasidone is indicated for the treatment of schizophrenia and schizoaffective disorder by the Food and Drug Administration, but several studies have suggested its effectiveness in the treatment of acute mania and bipolar disorder (2).

We report the case of a patient with bipolar disorder who had a history of tardive dyskinesia with typical neuroleptics. His symptoms had been latent for many years, including during a period of treatment with risperidone, but they reemerged with ziprasidone treatment.

**Mr. A was a 49-year-old man with bipolar disorder type I who suffered from continued mild to moderate chronic bipolar depression. He had been diagnosed with bipolar disorder over 12 years ago and had previously been treated with lithium, lamotrigine, carbamazepine, amitriptyline, desipramine, fluoxetine, paroxetine, citalopram, and oxcarbazepine. Mr. A also had a history of long-term treatment with traditional antipsychotics. During a 20-year period of treatment with thiothixene, Mr. A developed mild tardive dyskinesia. These symptoms disappeared when treatment was terminated and did not recur when he started to take risperidone. Mr. A took risperidone for 2 years but did not develop tardive dyskinesia.**

**Mr. A's medication regimen had been stable for several months and included lithium, clonazepam, ziprasidone, citalopram, and buspirone. Four months after Mr. A started taking ziprasidone, 100 mg/day, he began to experience symptoms of tardive dyskinesia again. Mr. A had seven consistently abnormal ratings of moderate to marked severity on the Abnormal Involuntary Movement Scale (AIMS) (3) over a period of 2½ months. He experienced moderate improvement in depression but continued to have symptoms of tardive dyskinesia after 7 months of treatment with ziprasidone.**

This case suggests that ziprasidone may be associated with the reemergence of tardive dyskinesia, particularly in a patient with several indicated risks, including long-term exposure to traditional neuroleptics and a diagnosis of bipolar disorder.

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## Paroxetine for Multiple Chemical Sensitivity Syndrome

TO THE EDITOR: Multiple chemical sensitivity syndrome is thought by some to be caused by extreme sensitivity to chemical "incitants" in concentrations that are ordinarily well tolerated (1). These patients typically report multiple somatic complaints and develop behavioral changes congruent with their beliefs about symptom causation. We report on a woman who was successfully treated for this condition with paroxetine.

**Ms. A was a 44-year-old woman who had developed a fear of strong chemical odors 2 years earlier after exposure to natural gas at work over a 2-week period. She reported episodic lightheadedness, a tingling of her lips, and an unsteady gait. She was moved to another part of the work site, and her symptoms disappeared. Several weeks later, after returning to her usual workstation, she developed diffuse muscle weakness, headache, nausea, and cloudy vision. An emergency medical team arranged for her to be flown to a tertiary care medical center 80 miles away. Results of a medical evaluation were unremarkable, and she was discharged the next day.**

**Over the ensuing months, Ms. A developed "reactions" when exposed to strong odors, which led her to alter her behavior. She stopped working and avoided attending church and shopping. She was diagnosed with multiple chemical sensitivity syndrome and subsequently obtained workers' compensation.**

**Ms. A was referred to the psychiatry department for evaluation. She had mild depression that did not fulfill criteria for major depressive disorder. She expressed a fear of chemical odors and described "reactions" that were identical to panic attacks. She was diagnosed with panic disorder with agoraphobia and was treated with paroxetine, 20 mg/day; her dose was gradually increased to 40 mg/day. Trazodone, 100 mg at bedtime, was prescribed.**

**Within 3 months, Ms. A was no longer depressed, and her "reactions" to chemical odors had stopped. She was able to shop unaccompanied and attend church. By her 5-month follow-up, Ms. A had returned to work and remained free of the "reactions." She has now been followed for nearly 4 years while receiving maintenance treatment with paroxetine, 40 mg/day, and trazodone, 100 mg at bedtime; she continues to be symptom free. She still believes that chemical odors induced her multiple chemical sensitivity syndrome.**

The treatment of patients diagnosed with multiple chemical sensitivity syndrome has been troublesome and has generally been the province of nontraditional medical practitioners. This case joins two others (2, 3) in showing that some patients diagnosed with multiple chemical sensitivity syndrome have an underlying psychiatric disorder that, when identified, responds to medication therapy.

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## Trauma 4,000 Years Ago?

TO THE EDITOR: Although evidence for symptoms of posttraumatic stress disorder (PTSD) in antiquity is scarce, I discuss evidence of trauma 4,000 years ago that has medical significance since it is, to my knowledge, the first description of PTSD symptoms in recorded history. This evidence extends the period of known PTSD symptoms from 350 years to 4,000 years ago (1).

Between 2027 and 2003 B.C., during the third dynasty of Ur, under the regime of King Ibisin, the Elamites from the east and the Sumerians from the west attacked the city of Ur and destroyed it (2). Reactions to the raid, plunder, slaughter, and the actual attack were recorded in cuneiform writing. The following verses describe psychiatric symptoms that resemble those of PTSD as presented in DSM-IV:

> The Sumerians and the Elamites, the destroyers, *made of it* thirty shekels.
>
> The righteous house they break up with pickaxe; the people groan.
>
> The city they make into ruins; the people groan.
>
> Its lady cries: "Alas for my city," cries: "alas for my house." (2, verses 242–245)
>
> In its lofty gates, where they were wont to promenade, dead bodies were lying about;
>
> In its boulevards, where the feasts were celebrated, *scattered they lay.*
>
> In all its streets, where they were wont to promenade, dead bodies were lying about;
>
> In its places, where the festivities of the land took place, the people lay in heaps. (2, verses 214–217)
>
> At night a bitter lament having been *raised unto me*,
>
> I, *although*, for that night I tremble,
>
> Fled not before that night's violence.
>
> The storm's cyclone like destruction—verily its terror has filled me full.
>
> Because of its [affliction] in my nightly sleeping place,
>
> In my nightly sleeping place verily there is no *peace* for me. (2, verses 95–99)

These verses describe documented exposure to the atrocities of war followed by the appearance of psychiatric symptoms 4,000 years ago. This evidence gives us the first glimpse of traumatic reactions in antiquity. These verses were written after exposure to a traumatic event, which was followed by characteristic symptoms, such as sleep disturbances, one of the most common PTSD symptoms (DSM-IV).

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## Postnatal Depression in India

TO THE EDITOR: I read with great interest the article by Vikram Patel, M.R.C.Psych., Ph.D., and colleagues (1). Although the study was well conducted and well written, there is an alternative way of interpreting its results and looking at the problem. Dr. Patel and colleagues concluded, "The study confirms our hypothesis that gender-based factors are important determinants of postnatal depression" (p. 46). They also stated, "It is plausible that the family's collective joy at the arrival of a male infant helps support the mother and negates the risk associated with other stressors" (p. 46).

First, I agree with Dr. Patel and colleagues that biological, social, and psychological factors are important determinants of postnatal depression. However, caution is needed when equating self-report data with a clinical diagnosis of depression. Screening instruments do not provide a clinical diagnosis of depression. Although the Konkani-language version of the Edinburgh Postnatal Depression Scale has been validated in the local study population (2), a cutoff score of 11 or 12 on the scale may overestimate postnatal depression (3). Use of a higher postnatal threshold could have provided a best estimate of the prevalence of depression. Some mothers scoring above the threshold will not have a depressive illness, and some below the threshold will.

Second, maternal education was found to be a significant protective factor against postnatal depression (relative risk= 0.5; $\chi^2$=4.4, df=12, p=0.03) (1, p. 45) and may have explained the precise mechanism of how poverty-related variables (low level of education, economic deprivation, and gender inequality that can lead to violence) and the infant's gender interacted differentially according to the gender of the infant. Limited intellectual resources for coping result in few psychological resources for developing a sense of control and mastery over the unpredictability of events (4). Therefore, mothers with a low level of education and limited intellectual resources for coping bear the weight of moral responsibility

as well, akin to guilt, which increases their psychological distress in this cultural setting, in which the preference for male children is deeply rooted. It is plausible that the arrival of a male infant negates this guilt; hence, there is a decrease in the probable cases of postnatal depression.

Finally, we appreciate the authors' efforts if their intention was to emphasize the fact that the needs of these mothers are primarily for appropriate social support of one sort or another. The ill-defined majority of psychologically distressed mothers are often left to muddle through well-meant social interventions orchestrated by vaguely skilled, empathic general practitioners, who are strongly versed in a medical style of response.

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## Dr. Patel Replies

TO THE EDITOR: Thank you for the opportunity to respond to Dr. Saravanan. As for his first point, I completely agree that the Edinburgh Postnatal Depression Scale is a screening measure, and like all screening measures, has imperfect sensitivity and specificity. We acknowledged this point in an earlier version of the article, but we removed it when we revised it for length. I should point out, however, that despite the Edinburgh Postnatal Depression Scale being a screening measure, it remains the most widely used case measure in epidemiological studies of postnatal depression. The cutoff score used in Goa, India, was validated against that of a structured psychiatric interview.

The author's second point seems to be an interpretation of the meaning of the associations we reported between risk factors such as low level of education and postnatal depression. His view seems fairly plausible but does not mean that our interpretation was incorrect.

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## Panic Disorder and Respiratory Tract Symptoms

TO THE EDITOR: In a recent article, Javaid I. Sheikh, M.D., M.B.A., et al. (1) found that female respondents with panic attacks were more likely to experience respiratory-related difficulties than male respondents with panic attacks. In an earlier article (2), we did not find more visits to pulmonary doctors by patients with panic disorder, but we did find that 44% of the patients with panic disorder visited ear, nose, and throat specialists in the past year. Also, we recently found a high incidence of allergies in patients with panic disorder (3). Moreover, the patients with panic disorder and allergies endorsed significantly more respiratory symptoms on the Hamilton Anxiety Rating Scale than did the nonallergic patients with panic disorder (3). We do not have data regarding gender and these variables, but there were 52% women and 48% men in the study.

These findings suggest that in subjects with panic disorder, studies should identify gender, allergy status, and respiratory symptoms. Studies of carbon dioxide sensitivity in allergic female subjects with panic disorder would be of interest.

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## Dr. Sheikh and Colleagues Reply

TO THE EDITOR: We thank Dr. Kennedy for her thoughtful comments and suggestions for future investigations with panic disorder patients concerning the relationship of gender, allergies, and respiratory symptoms. Our secondary analyses of National Comorbidity Survey data did not extend to potential pulmonary disorders or to specialty medical use associated with panic-related respiratory disturbance. However, Dr. Kennedy's suggestion of heightened panic response in allergy patients is consistent with Dr. Klein's observations (1) that hypersensitive false-alarm mechanisms underlie the dyspneic response observed during panic attacks. We are aware of two studies that have examined panic response in patients with multiple chemical sensitivity and idiopathic environmental intolerance (2, 3). Binkley et al. (2) found that four of five self-identified "chemically sensitive" patients who complained of respiratory complaints met diagnostic criteria for panic disorder. Further, patients with multiple chemical sensitivity syndrome responded with panic symptoms when administered sodium lactate, a well-known panicogen, but not when they were administered saline solution. We encourage Dr. Kennedy to further investigate the potential for undetected panic disorder in allergy patients and the possibility for converging pathophysiologies between these two disorders.

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## EEG Changes With Antipsychotic Drugs

TO THE EDITOR: In a study of the EEG changes associated with antipsychotic drug treatment, Franca Centorrino, M.D., et al. (1) reported that the "EEG abnormality risk varied widely… [and was] particularly high with clozapine and olanzapine, moderate with risperidone and typical neuroleptics, and low with quetiapine" (p. 109). The authors' use of "abnormality" to describe changes in the EEG records should be criticized. The term reflects a practice in clinical neurology that is not applicable to describing the effects of psychoactive drugs (2).

In psychiatric practice, adequate serum clozapine levels are deemed necessary for its beneficial effects. These are not characterized as "abnormal" unless they exceed safety levels. EEG changes also vary with serum levels and are as necessary as adequate serum levels for clinical efficacy (3, 4). "Abnormality" suggests a deleterious effect, and from reading the report's summary sentence as quoted, the reader would conclude that quetiapine has a favorable balance of toxicity over clozapine and risperidone. The reverse is probably true—that the failure of quetiapine to elicit EEG changes probably reflects a lesser clinical effect.

Stevens (5) presented a cogent argument for evaluating the EEG slow waves of clozapine as evidence of its therapeutic activity. She found the centrencephalic effects of clozapine to be the basis for its clinical efficacy and advised that these changes be heralded rather than decried. A parallel relationship of EEG effects is found in studies of ECT, in which electrophysiologic slowing reflects its therapeutic effects (6). Failure to elicit interseizure EEG slowing during an ECT course is associated with poor clinical outcome. The development of EEG slow-wave activity is a necessary part of the ECT process, and when these changes are absent, so too are the clinical benefits.

The term "abnormality" comes from a neurologic literature that uses visual impressionistic methods to assess EEG records. But psychoactive drugs induce subtle changes that are not appreciated in visual analysis. They require quantitative digital computer processing for true estimates of effect (2). Describing the EEG changes associated with psychoactive drugs as "abnormal" or "normal" is misleading. Disregarding the excellent technical methods of analysis for EEG that match the advances in other brain imaging methods degrades the science.

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## Dr. Price and Colleagues Reply

TO THE EDITOR: We appreciate Dr. Fink's letter and would like to respond. Without suggesting a better alternative, he states that the term "abnormality" used to describe changes in EEGs is a term used in clinical neurology that is not applicable to describing the effects of psychoactive drugs. We respectfully disagree.

Since the EEG was invented in 1929, the term "abnormality" has been used by convention as applying to any EEG that is not considered normal. It is well recognized that abnormal EEGs may have no deleterious functional consequences. Likewise, in our article, we did not imply that the EEG abnormalities suggested a deleterious clinical effect. In fact, we stated that "The present study was unable to specify the clinical significance of EEG abnormalities encountered….Prospective studies are required to define the clinical significance of specific types and levels of EEG abnormalities" (p. 114). We commented that our study "encourage[s] prospective EEG analyses before and during treatment with specific drugs and objective ratings of clinical changes" (p. 114).

We also acknowledged Stevens's 1995 article, among others (see references 34–37), regarding the as-yet-unsettled controversy surrounding abnormal EEG changes possibly heralding the efficacy of clozapine.

The main points in our article were that

1. Various psychoactive drugs may alter the EEG architecture in predictable ways.

2. These EEG abnormalities can be seen by routine EEG inspection without requiring computer processing.

3. The interpretation of EEGs must be careful to avoid misattribution of these psychoactive drug changes to underlying disease.

4. The use of EEGs in psychiatric populations should be reinvigorated given their possible implications regarding diagnosis, function, and prognosis.

It is for these reasons that we defend the use of the term "EEG abnormalities" and disagree that it "degrades the science."

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## Pathological Examination in Vascular Dementia

TO THE EDITOR: We read with great interest the article by Gabriel Gold, M.D., and coauthors (1). Since there is a remarkable lack of data on the neuropathology of vascular dementia, studies aimed at evaluating the pathological findings in pa-

tients with dementia and cognitive impairment are badly needed.

Dr. Gold and co-workers compared the postmortem diagnoses of dementia types with those clinically reached by the application of four well-known sets of criteria for vascular dementia (those from DSM-IV, ICD-10, the State of California Alzheimer's Disease Diagnostic and Treatment Centers [ADDTC], and the National Institute for Neurological Disorders and Stroke—Association Internationale pour la Recherche et l'Enseignment en Neurosciences [NINDS-AIREN]). The authors reported that the sensitivity of these clinical criteria, when compared to the gold standard of postmortem examination, ranged from 0.20 (NINDS-AIREN criteria) to 0.70 (ADDTC criteria), while the specificity showed somewhat higher values, ranging from 0.78 to 0.93. We would like to contribute to the discussion with some comments.

First, as acknowledged by the authors, there are no established and validated pathological criteria for vascular dementia. In their study, the attribution of a patient to the vascular dementia group was based on the finding of multiple macroscopic and microscopic cortical infarcts involving three or more cortical areas exclusive of the visual cortex. Lesions confined to the subcortical structures were not taken into account; this was obviously arbitrary. As is largely accepted today, "vascular dementia" encompasses a wide spectrum of conditions, only some of them related to the occurrence of multiple cerebral infarcts. Unfortunately, almost all current criteria, while recognizing this aspect, outline clinical features (the presence of major cerebrovascular events) that are mostly related to the occurrence of large cerebral infarcts. As rightly stated by the authors, current criteria mainly identify cases of so-called "multi-infarct dementia." It is disappointing that these cases do not appear to be the most prevalent in the population, being probably numerically surmounted by cases characterized by the presence of subcortical lesions (multiple or strategic lacunar infarcts and diffuse white matter lesions) mainly linked with disease in the small vessels (2–4).

Second, cases of subcortical vascular dementia are probably the most difficult to clinically distinguish from degenerative cases, given the lack of a history of stroke in many instances and progressive cognitive decline. Only a thorough clinical and neuropsychological evaluation, perhaps with the help of neuroimaging, may clarify this distinction. That is seldom the case in retrospective and epidemiological studies. Accordingly, the sensitivity and specificity of current criteria could be even lower in examinations of patients with subcortical lesions.

A final consideration concerns the role of neuropathology in the field of dementia. Since dementia is a pure clinical definition, can the pathological examination be considered a true gold standard in this field? By no means; neuropathology has a great role in defining the lesions present in patients with cognitive decline. However, we feel that we are far from finding the precise structural correlate of dementia in the brain. In many instances, dementia derives from a functional rather than from an anatomical alteration. In other instances, the discovery of cerebral lesions is not reflected in clinically evident alterations. Accordingly, the diagnosis of dementia should remain essentially clinical. Notwithstanding these facts, there is a tremendous need to descriptively and systematically study from the pathological viewpoint the types, extent, location, and possible coexistence of cerebral lesions in cases of cognitive decline. However, agreement should be reached regarding what lesions are to be considered as vascular. Neuropathologists are called upon to merge their efforts with those of clinicians and neuroradiologists to better define the vascular burden on the brain.

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## Dr. Gold and Colleagues Reply

TO THE EDITOR: Drs. Pantoni and Inzitari make several interesting points regarding the validity of clinicopathological correlations in vascular dementia. They stress the great difficulty in diagnosing subcortical vascular dementia and rightly suggest that the sensitivities and specificities of the criteria for general vascular dementia may be lower for subcortical diseases than for multi-infarct dementia, which was the main focus of our study. Although subcortical lesions are particularly common in aged brains, their clinical significance is still controversial. In this light, it would be meaningful to explore the performance of newly proposed specific criteria for subcortical vascular dementia (1).

It is important to note that the neuropathological criteria we chose to diagnosis patients with multi-infarct dementia were far from arbitrary. As indicated in the text, we applied a restrictive definition (the presence of both microscopic and macroscopic infarcts in at least three or more associative neocortical areas exclusive of the secondary visual cortex and the absence of significant other dementia-related pathology) that could lead to broad agreement that such cases were indeed instances of vascular dementia. We agree that the diagnosis of dementia itself must be clinical (all of our patients had clinical dementia); however, postmortem examination of the brain has a key role in identifying the underlying pathology associated with the clinical expression of dementia. In this respect, neuropathology must remain the gold standard for the validation of clinical criteria. Furthermore, examples of numerous clinicopathological studies of Alzheimer's disease have demonstrated that it is possible to establish valid correlations between the progression of neuropathological changes and both the severity of cognitive decline and the specific pattern of affected cognitive domains (2, 3). Demonstrating such relationships is not yet possible in vascular dementia. In order to address this issue, there is indeed a strong

need to develop consensual and validated neuropathological criteria that can also reflect the amount of vascular burden for each of the various subtypes of vascular dementia.


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## Thyroid Hormones and Antidepressant Response

TO THE EDITOR: We read with great interest the review and meta-analysis by Lori L. Altshuler, M.D., et al. (1) about thyroid hormone supplementation accelerating tricyclic antidepressant response. One possible explanation is that the patients treated with tricyclic antidepressants in those studies may have had overt or subclinical hypothyroidism whose correction with triiodothyronine ($T_3$) allowed them to overcome impaired response to tricyclic antidepressants.

In a previous study (2), we showed that subclinical hypothyroidism is not rare among patients with episodes of major depression (5.3%) and that serum concentrations of thyrotropin, or thyroid-stimulating hormone (TSH), at or above the upper 25th percentile of the normal reference range may be associated with characteristics of severe major depression. Consequently, we systematically measured TSH, thyroxine ($T_4$), and $T_3$ serum levels in 101 consecutive patients hospitalized for episodes of major depression. The Hamilton Depression Rating Scale was administered at entry and after 28 days of antidepressant therapy. All patients gave written informed consent. The observer assessing scores on the Hamilton depression scale was unaware of serum thyroid hormone test results. Nine patients (9%) had serum TSH concentrations at or above the upper 25th percentile of the normal reference range (group A); only three (3%) had serum TSH concentrations higher than the upper limit of the normal reference range. All nine of these patients were women, and this sex distribution was significantly different from that for patients with serum TSH concentrations below the upper 25th percentile of the normal reference range (group B) ($\chi^2$=5.47, df=1, p<0.02). Group A had a higher serum TSH concentration than did Group B (mean=4.31 μIU/liter, SD=3.27; mean=1.13 μIU/liter, SD=0.55, respectively) (Mann-Whitney z=4.93, p<0.001) and a higher $T_3$ concentration (mean=3.44 ng/ml, SD=7.10; mean=0.85 ng/ml, SD=0.22) (Mann-Whitney z=1.65, p<0.10) but not a higher serum $T_4$ concentration (mean=10.14 ng/ml, SD=1.02; mean=10.71 ng/ml, SD=2.20).

The scores on the Hamilton depression scale were similar at entry (group A: mean=21.89, SD=5.93; group B: mean=23.21, SD=5.33), but group A's response to antidepressant treatment (tricyclic antidepressants, N=3; selective serotonin reuptake inhibitors, N=3; serotonin/norepinephrine reuptake inhibitors, N=5) at day 28 was significantly less than for group B (decrease in score on the Hamilton depression scale—group A: mean=8.67, SD=6.86; group B: mean=14.70, SD=8.12) (analysis of covariance: F=4.22, df=2, 98, p<0.05). The mean ages, frequencies of previous suicide attempts, and rates of recurrent depression were not different between the groups.

The definition of the normal reference range of serum TSH concentrations is established in healthy subject populations without clinical signs of thyroid dysfunction. It is not known whether this "endocrinological" reference range can be applied to patients with depression. High-normal serum TSH concentrations are associated with an exaggerated TSH response to thyrotropin-releasing hormone in depressed patients (3), and subtle thyroid axis modifications may account for up to 36% of the variance in antidepressant treatment outcome (4). We suggest that screening for serum TSH concentration in patients with major depression is helpful in identifying those who have concentrations at or above the upper 25th percentile of the normal reference range. The supplementation of antidepressant therapy by thyroid hormones is particularly indicated in these patients.


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## Psychotic Recurrence After Antipsychotic Discontinuation

TO THE EDITOR: Michael Gitlin, M.D., et al. (1) made an extremely important contribution to our field by demonstrating that essentially all individuals who have a remission of a first episode of schizophrenia will have a recurrence if they discontinue antipsychotic medication. Despite this striking result, the authors did not suggest that this new finding should translate into a strong recommendation for long-term antipsychotic maintenance treatment. Why were the authors reluctant to make such a recommendation?

The authors acknowledged that the study was undertaken to evaluate a targeted medication approach in a group with recent-onset schizophrenia. While it is now clear that targeted medication approaches should not be generally recommended for patients who have had multiple episodes of illness (2), this study should raise similar concerns about its use in first-episode patients in remission. The fact that only 13% of the patients needed to be rehospitalized in the first 2 years

of no medication is hardly reassuring. It is not the risk or cost of hospitalization that argues for continuous treatment, nor is it the hypothetical risk of psychosis-induced neurotoxicity. It is the need to spare individuals with schizophrenia and their families from the terrible suffering and disruption to their lives that all too frequently accompany such recurrences. Hospitalization is too crude a measure of outcome. Assessments of outcome need to take into account the degree to which patients are able to function, as well as their quality of life and risk of suicide in the long term.

Interpretation of the study by Dr. Gitlin et al. was also greatly limited by the absence of a control group assigned to continuous treatment. We do not know whether patients who discontinue their medications achieve the same degree of recovery in the long term as those who receive continuous medication. The authors gave the impression that if a recurrence is identified early, it can be easily treated and the person can be rapidly returned to his or her previous level of functioning. No data are provided to support this notion. To the contrary, current evidence suggests that each relapse from a remitted state may be associated with a substantial risk of incomplete remission and persisting disability (3).

Given this compelling new evidence of a 100% risk of recurrence and the absence of evidence that targeted treatment carries lower medical risks than continuous treatment, should we not give the majority of our first-episode patients in remission a clear recommendation to keep taking medication? That some may choose to do otherwise is understandable. We will at least have given them our best advice.

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## Dr. Gitlin and Colleagues Reply

TO THE EDITOR: We appreciate Dr. Zipursky's comments about our recent article. He asks a key question: given the high rate of return of psychotic symptoms in our group of recent-onset schizophrenia patients during a trial period without maintenance medication, why not simply recommend continuous treatment, even after 1–2 years of maintenance medication, while acknowledging that some (or many) patients will not follow that advice? Avoiding even nonhospitalized recurrence of psychosis is an important goal that we did not mean to minimize in the discussion of our results. Our data suggest that the exacerbation or relapse rate is high (78% within 1 year and 96% within 2 years) for carefully diagnosed patients, even after an initial period of maintenance medication.

We certainly hope that the findings of this study will be shared with first-episode patients who are weighing the costs and benefits of long-term continuous medication therapy. All decisions in medicine are, of course, made by using risk-benefit comparisons. Our study was conducted before atypical antipsychotics were available for everyday clinical treatment of recent-onset patients, so the risk of tardive dyskinesia was a dominant component of any discussion of long-term treatment. As the risks (e.g., chances of severe side effects) of antipsychotic medications decrease with advances in the formulation of atypical antipsychotics, the scales tip in favor of advocating longer periods of continuous medication treatment after an initial episode.

Despite important psychopharmacological advances, atypical antipsychotic agents are unfortunately not risk free. Various medical concerns—especially those related to alterations in lipid profiles and new-onset diabetes mellitus—and subjectively distressing side effects, such as sedation, weight gain, and sexual dysfunction, make a decision to undertake long-term treatment after a first episode worthy of discussion rather than an automatic recommendation. Indeed, weighing the benefits and risks of a specific treatment is part of the right of choice that patients have and reinforces the trust relationship so critical to open, honest communication between doctor and patient. Therefore, we did not make a universal recommendation for patients with recent-onset schizophrenia.

We also know that approximately one-half of all schizophrenia outpatients will be significantly noncompliant with their antipsychotic medication over a 1-year period. Rather than having patients resort to the overt (or covert) nonadherence to prescribed medication that typically results in their dropping out of treatment altogether, we would rather see the patient and psychiatrist agree to try a period without medication with close clinical monitoring if patients do not accept the recommendation of long-term continuous medication.

We agree with Dr. Zipursky that a finer-grained analysis of the functional consequences of a return of psychotic symptoms would be illuminating, particularly if this could be done within a randomized study design that would allow firmer conclusions to be made. Since neurocognitive impairment is more strongly and consistently related to functional impairment than positive symptoms (1), such studies should include consideration of any changes in neurocognitive impairment over time.

As new antipsychotics are developed with greater efficacy on multiple dimensions of schizophrenic psychopathology (including negative symptoms) and more benign side effect profiles, recommendations for continuous long-term treatment after a first schizophrenic episode for all patients may become the norm. For now, however, we believe that case-by-case clinical consideration, within the context of a truly collaborative patient-doctor relationship, is optimal.

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## Moral Dilemmas Faced by Psychiatrists

TO THE EDITOR: The article by Stephen A. Green, M.D., M.A., and Sidney Bloch, M.D., Ph.D. (1), provides psychiatrists with a valuable review of the moral dilemmas faced by practitioners working in dysfunctional administrative environments. The article systematically highlighted utilitarian and existential aspects of these quandaries. However, an important third perspective, Kantian ethics, remains undeveloped.

As Drs. Green and Bloch explicitly pointed out, utilitarian ethics can be understood as a program of maximizing gratification for the greatest number of people. Hence, utilitarianism is most germane to the relationship between efficiency and equity in the delivery of mental health care. Existential ethics, on the other hand, may be seen as an elevation of an individual's autonomous moral courage over the collective dictates of his or her social milieu. Thus, existentialism implicitly throws light on the struggle of the individual psychiatrist to maintain professional autonomy.

Kantian morality distinguishes itself from both utilitarianism and existentialism by assigning priority in ethical valuation to a peculiar combination of will and social logic. The first version of Kant's categorical imperative erected the following standard: we should act only in a manner such that if all others acted similarly, then no self-contradiction would result. Hence, Kant's ethical reasoning, like utilitarianism and unlike existentialism, drew on collective considerations. Kant added that moral value arises only from categorically mandated acts that require a denial of gratification. Hence, unlike utilitarians and like existentialists, Kant devalued gratification and instead opted for moral discipline. Elements of Kant's categorical imperative, therefore, are both like and unlike other ethical frameworks, while Kantian ethics in totality is unique.

Kant's standard provides a rigorous yardstick by which practitioners can gauge the merits of their own acts. Psychiatrists working in flawed systems might contemplate coping responses, such as adjusting diagnoses to obtain insurance coverage for endangered patients, openly challenging destructive administrative policies, and separating completely from pernicious systemic structures. Before acting, the Kantian clinician may first take the opportunity to imagine the potential consequences should the action be universalized. Predicted self-defeating contradictions can then serve as a moderating map of possible ethical outcomes.

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## Drs. Green and Bloch Reply

TO THE EDITOR: We very much appreciate Dr. Mender's kind and thoughtful remarks on our article. We have no quarrel with a Kantian perspective and appreciate Dr. Mender's marshaling of appropriate arguments. He correctly portrays one elaboration of the categorical imperative: highlighting the collective aspects of that elaboration. He does not mention a crucial second iteration of Kant's position—namely, to treat individuals as ends, not as means. We could argue that flawed systems fail to treat people as "ends" and are inherently neglectful in this regard. Thus, establishing categorical imperatives for psychiatric practice is undoubtedly a noble goal and could possibly assume the form advocated by Dr. Mender. Clearly, several ethical justifications are available for what we argue. Our basic concern is that practitioners strive to correct or improve flawed systems. Any theoretical framework that can contribute to promoting that goal is welcome.

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## Remembering Max Schur

TO THE EDITOR: I would like to add some personal recollections to the recent Image in Psychiatry about Max Schur by Stephen M. Wittenberg, M.D., and Lewis M. Cohen, M.D. (1). My association with Dr. Schur largely consisted of being in analysis with him for almost 10 years, from November 1959 until his death in early October 1969. During these years, analysis became a powerful intellectual and emotional force in my life, teaching me new insights about myself (sometimes quite painful) that then often enabled me to make changes in relationships with my father, mother, wife, and two young daughters and to begin to develop the professional identity of a psychoanalytically oriented psychotherapist.

At this time I also formed an interest in the biography of Charles Darwin and began transcribing many of Darwin's unpublished letters. And after hearing Dr. Schur lecture on his physician-patient relationship with Freud and then on a study of unpublished letters that showed Freud's early negative thoughts about his friend and colleague Wilhelm Fleiss (2–4), I was influenced to think about Darwin's protracted illness and his ambivalent feelings for his geological mentor, Charles Lyell. Years later, having gained an intimate knowledge of Darwin's life, I published a book on his illness (5), followed by an essay delineating the mental conflicts he experienced with Lyell and others over his evolutionary theory (6).

I continue to be guided in my personal and professional life by the insights I learned in analysis. I often remember the attributes of Dr. Schur: his vitality, sense of humor, curiosity about many things, medical and psychological acumen, and empathy (shaped, I believe, by years of medical and psychoanalytic work) for the sufferings of the patients he treated.

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