Letters to the Editor

Recurrent Priapism During Treatment With Clozapine and Olanzapine

TO THE EDITOR: We report a case of priapism after the administration of olanzapine in a patient who on two previous occasions had had priapism that was associated with clozapine treatment. The first case of priapism associated with atypical antipsychotics was reported in 1992 and involved clozapine (1). Subsequently, at least five other reports of clozapine-associated priapism have appeared in the literature. The first reported cases of priapism after the administration of olanzapine were published in 1998 (2, 3). Many medications have been associated with priapism, which is thought to be related to α-adrenergic blockade. Olanzapine has a pharmacological profile similar to that of clozapine, with a high affinity for dopamine D_1, D_2, and D_4, serotonin (5-HT) 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3, muscarinic, α_1-adrenergic, and histamine H_1 receptors. This medication is increasingly used because of its proven antipsychotic activity and favorable side effect profile.

Mr. A was a 43-year-old man diagnosed with schizoaffective disorder of the bipolar type. He began clozapine therapy for refractory psychosis, which resulted in near-complete remission of his psychotic symptoms. However, he later experienced two episodes of prolonged painful erection, which lasted approximately 12.0 and 13.5 hours. Mr. A's clozapine treatment was discontinued, and during the next 2 years his condition was stabilized with olanzapine, divalproex, and thiothixene. His medical records indicated that an adequate response was not achieved with the combination of divalproex and olanzapine or divalproex and thiothixene.

Mr. A was then hospitalized for exacerbation of his psychosis. He had been noncompliant with his psychotropic treatment for 3 weeks before admission. At admission, his treatment regimen was reinitiated, as previously prescribed, with 25 mg/day of olanzapine, 1000 mg/day of divalproex, and 5 mg/day of thiothixene. The next morning he awoke with a painful erection. With conservative drug management, the priapistic episode began to remit after 5 hours. Mr. A's penis returned to normal flaccidity after 8 to 10 hours. His dose of olanzapine was discontinued, and he was stabilized with 25 mg/day of thiothixene. This adverse event was reported to the manufacturer and the Food and Drug Administration.

This case represents the third published report of priapism associated with the administration of olanzapine of which we are aware. Although thiothixene has been reported to cause priapism, as have many other conventional antipsychotics, the patient did not experience an episode during his stable period with an increased dose of thiothixene. None of his other medications (divalproex, gemfibrozil, or glyburide) have been reported to cause this adverse event. His three priapistic episodes may indicate a sensitivity to the shared pharmacologic properties of clozapine and olanzapine. His most recent priapism was most likely due to the α-adrenergic-blocking capacity of olanzapine. We believe this case may be of heuristic value and caution clinicians who prescribe olanzapine to men with a history of priapism.

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Olanzapine and Panic Attacks

TO THE EDITOR: Panic disorder usually responds favorably to therapy with selective serotonin reuptake inhibitors, tricyclics, or benzodiazepines (1). However, there are a number of patients whose disorders are refractory to standard treatment and whose management represents a challenge. We present the cases of two patients with treatment-resistant panic disorder who responded to treatment with olanzapine.

Mr. A, a 32-year-old man without comorbid disorders, was seen for a panic disorder of 4 months' duration. His panic attacks were initially nocturnal but later appeared at any time of the day. Mr. A was treated consecutively with 40 mg/day of paroxetine for 2 months, 200–300 mg/day of fluvoxamine for 6 months, and 150 mg/day of clomipramine for 2 months. He also received concomitant alprazolam, 2–4 mg/day, during this 10-month period. Mr. A was later hospitalized for suicidal thoughts and discharged 1 month later on a regimen of 2 mg/day of clonazepam, 15 mg/day of perphenazine, 30 mg/day of ketazolam, and 150 mg/day of venlafaxine. Five days after his discharge, his perphenazine dose was replaced with olanzapine, 7.5 mg at bedtime.

Two weeks later Mr. A was much calmer and sleeping well, but he had mild morning anxiety. His olanzapine dose was increased to 12.5 mg/day, and his venlafaxine was replaced with nefazodone, up to 600 mg/day. Mr. A improved progressively during the following weeks, and clonazepam and ketazolam were discontinued. After 4 months Mr. A was free from panic attacks, left his house alone, and enjoyed leisure activities.

Ms. B was a 40-year-old woman who was seen for panic attacks with agoraphobia that had lasted for 2 years. She had intense somatic worries and was away from work on sick leave. She had no comorbid conditions. She received treatment with 40 mg/day of paroxetine plus 2–3 mg/day

of alprazolam for 6 months. She then received 400 mg/day of nefazodone, plus 10 mg/day of diazepam, 50 mg/day of sulpiride, and 1 mg/day of alprazolam for 6 months with no improvement. Then a combination of 12 mg/day of perphenazine, 75 mg/day of amitriptyline, and 10 mg/day of diazepam was tried. After 5 months, 10 mg/day of olanzapine was begun, while maintaining her doses of amitriptyline (75 mg/day) and diazepam (10 mg/day). After 15 days Ms. B was feeling calmer and in a better mood. After 2.5 months Ms. B was being treated with 10 mg/day of olanzapine, 50 mg/day of amitriptyline, and 2.5 mg/day of diazepam; she had had no crises since she began olanzapine treatment and had started going out alone.

The American Psychiatric Association's practice guideline for panic disorder (1) states that there is no evidence to support the use of typical antipsychotics for anxiety disorders and that the neurological risks outweigh the potential benefits. There are reports of olanzapine's efficacy in bipolar disorder and depression (2), but we believe this is the first report in the literature suggesting a favorable response in panic disorder. The mechanism of action could be through serotonin type 2 receptors. Given the benign side effect profile of olanzapine compared to that of conventional neuroleptics, we believe that its use could be justified in cases of panic disorder that are refractory to conventional treatment.

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Vitamin B_{12} Deficiency Manifested as Psychosis Without Anemia

TO THE EDITOR: Vitamin B_{12} deficiency typically appears as lower-extremity paresthesia or ataxia, most often with concurrent folate deficiency and megaloblastic anemia (1). We report the case of a patient who was deficient in vitamin B_{12} and was diagnosed with psychosis in the absence of folate deficiency or anemia.

Ms. A was a 52-year-old woman with a 3-month history of acute paralysis of the lower extremities and a 1-month history of paranoid delusions of persecution, delirium, and severe agitation. Ms. A had no significant prior medical or psychiatric history nor any history of drug or alcohol use. Up until 3 months before, she had been in excellent health, happily married, and employed. Ms. A had consulted a neurologist at the onset of her weakness in the lower extremities and was diagnosed with multiple sclerosis. Over the next several weeks, she was placed on a regimen of medications including carbamazepine, amitriptyline, tramadol, diazepam, prednisone, thiamine, and multivitamins. Despite this, her weakness worsened. She required a cane, then a walker, and finally a wheelchair to get around just 3 months after the onset of her symptoms.

In the month preceding our interview, Ms. A's neurological symptoms had been overshadowed by the acute onset of psychiatric symptoms. She had become increasingly agitated and short tempered with her family, on several occasions throwing furniture at them and once trying to exit a moving car to escape them. She had even called the police several times to report her family for attempting to poison her food. Her family eventually brought her to the emergency room of a state mental health center, where in her first interview with us, she appeared disheveled and uncooperative and had a labile mood and affect. She also showed evidence of delirium, with waxing and waning alertness, anger, and loss of aspects of both her long- and short-term memory.

An examination revealed large bilateral patches of desquamated skin on her feet and normal oral mucosa. Her cranial nerves were intact. Ms. A was, however, unable to stand unassisted. A right Babinski reflex was present, as well as a bilateral loss of proprioception, vibration, and sensation of light touch and pain in the lower extremities. Strength and reflexes in the lower extremities were bilaterally symmetric and grossly diminished. Results of tests of the upper extremities were normal. Ms. A's CBC results were normal, as were her serum folate and iron levels. Serum vitamin B_{12} levels were measured and were found to be markedly diminished—less than 9 pg/ml (normal=200–950 pg/ml).

Ms. A was diagnosed with subacute combined spinal cord degeneration and psychosis due to severe vitamin B_{12} deficiency. She received intramuscular vitamin B_{12} injections and was transferred to a medical facility. Subsequent test results revealed intrinsic factor and parietal cell antibodies in her serum, as well as elevated levels of methylmalonic acid (23 μmol/liter; normal, <0.4 μmol/liter) and homocysteine (26 μmol/liter; normal, <13 μmol/liter). An endoscopic gastric biopsy revealed atrophic gastritis with prominent intestinal metaplasia.

The etiology of this patient's vitamin B_{12} deficiency was classic pernicious anemia; however, when she was seen her most prominent symptom, anemia, was masked. The most likely explanation is that the patient had received folate supplementation during one of her previous emergency room visits or hospitalizations, which corrected for her hematological disease but allowed neurological damage to continue at an accelerated rate. This case reinforced for us the importance of proper follow-up on routine laboratory tests before the implementation of any therapy, even one seemingly as benign as vitamin supplementation (2). In this case, the lack of hematological findings on a routine CBC helped mask what should have been a simple diagnosis of vitamin B_{12} deficiency. Adding to the confusion over the cause of the psychosis, the patient had a prior diagnosis of multiple sclerosis (which ultimately proved to be inaccurate), as well as a history of recent steroid use.

Several factors, however, should have suggested an organic cause for this patient's psychosis: her symptoms included disorientation and delirium, had a sudden onset, were accompanied by significant medical morbidity, and were unaccompanied by any history of drug abuse or family or prior history of psychiatric illness. Once the organic nature of her psychiatric illness was realized, the patient was given vitamin B_{12} supplementation. Within 2 days the strength in her lower extremities had improved. Within 2 months her psychosis was

completely resolved, and her only remaining deficit was unilateral weakness of the lower extremities and ataxia, although it was considerably less severe than when she was first seen. We can only assume that had her psychosis been recognized and treated as a symptom of vitamin B_{12} deficiency much earlier, a complete reversal of her symptoms might have been expected (3, 4). As it is, only time will reveal whether her remaining neurological deficits are temporary.

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Older Patients and Health Care Utilization

TO THE EDITOR: A recent article by Helen C. Kales, M.D., et al. (1) draws attention to the increased inpatient medical/psychiatric resources utilized by patients discharged with comorbid diagnoses of dementia and major depression. The article represents a significant step forward in view of the paucity of literature on the subject.

We would like to point out, however, some limitations in the study design used in addressing the question of prognosis, in terms of the utilization of health care services, in patients discharged with diagnoses of dementia alone (group 1), dementia and major depression (group 2), and major depression alone (group 3). Among the key aspects of the study design that were needed to answer the question, perhaps the most significant limitation was the lack of "a representative and well-defined sample of patients at a similar point in the course of the disease."

The discharge diagnoses from a routine administrative database such as that used by this study are likely to be of limited accuracy. Various biases are likely to have affected them (for instance, the comorbid diagnosis of major depression may have been more likely to be given during a psychiatric admission than during a medical one, and more diagnoses may be listed for longer inpatient stays).

Also, since the database could not provide information about the severity and duration of the dementia, the patients in group 1 might have been at a more advanced stage of illness. This possibility is supported by the fact that the patients in group 1 were older, had a higher mortality rate, and were nonsignificantly more likely to be discharged to nursing homes (1,315 of 5,060) than the patients in group 2 (56 of 265) (Pearson's χ^2=3.11, df=1, p=0.08). If so, they would be expected to have not only a different pattern of health care utilization but also a diminished ability to report their depressive symptoms. A partial improvement could have occurred in the period from the first recorded diagnosis of dementia to the follow-up.

Of the outcome measures on which the groups were compared, the only ones on which groups 1 and 2 differed significantly were those pertaining to psychiatric readmissions. The issues discussed could have substantially affected these findings but were not addressed in the study design, analysis, or discussion. We hope that Dr. Kales et al., having drawn attention to this important finding, will conduct a prospective study comparison of these groups that takes into account the biases that can operate in such a study of prognosis (2).

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Dr. Kales and Colleagues Reply

TO THE EDITOR: We agree that the patient's stage of dementia might affect the degree and type of health care utilization, as well as possibly influencing the ability to report depression. Certainly as cognitive impairment worsens, patients may be less able to articulate changes in affective states.

Depression in dementia has often been thought of as secondary to psychological awareness of decreasing cognitive capacity, hence the impression that depression tends to occur in mild dementia. However, studies have found major depressive disorder even in advanced dementia in which patients were considered beyond the point of self-awareness (1). Depression itself has an adverse effect on functional ability. Thus, in moderate dementia the added burden of depression can determine whether the activities of daily living can be performed or not (and can also affect dementia staging) (2).

Furthermore, the distinction between behavioral manifestations of depression and of dementia itself (e.g., agitation) can be difficult. Conceivably, patients in our coexisting dementia and depression group may have in fact been at a *more* advanced stage of dementia, in which depression or other behavioral problems became harder to separate. This would make this group a more behaviorally disturbed group, perhaps driving higher psychiatric inpatient utilization than in the group with dementia alone.

Although we attempted to account for medical comorbidity with the mean number of medical diagnoses, this was at best a rough estimate and not as precise as actual comorbidity ratings would have been had they been available. Accordingly, the concerns that Drs. Mago and Berlin raise (that patients with dementia alone had a higher mortality rate, were older, and may have been more likely to have nursing home discharges) may actually be more related to the severity of comorbid medical illnesses than to the stage of dementia.

We agree that there are limitations to the use of retrospective databases. However, these databases also present certain advantages, including the ability to examine longitudinal outcomes for large numbers of patients. In our view, the limitations of the study are outweighed by two significant contributions: 1) this is by far the largest group of patients with

coexisting dementia and major depression ever described to our knowledge, and 2) it is the first study to examine health care outcomes for this group in detail, compared to patients with either disorder alone. Furthermore, we believe that the results of the study inform further prospective work.

We concur that a prospective group study is needed to sort out the noted concerns. We are in the process of conducting such a study. With our current study, we are paying close attention to the stage of dementia, as well as to other factors that might confound outcomes and prognoses in patients with coexisting dementia and depression.

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"Cognitive Dysmetria" in Schizophrenia

TO THE EDITOR: We read with great interest the results of a recent positron emission tomography (PET) study by Benedicto Crespo-Facorro, M.D., et al. (1). Using a word list recall paradigm, the authors were able to demonstrate decreased activation of widespread cortical-subcortical neural circuitry in unmedicated patients with schizophrenia. There was relatively decreased blood flow in the left rostral supplementary motor area—a striking finding. Drs. Crespo-Facorro et al. concluded that this hypoactivation could reflect a deficit of internal response selection and the timing/sequencing of mental functions, which is closely related to the impairment of self-generated willed actions in schizophrenia (2).

However, an alternative explanation may also arise. In a PET study (3), McGuire et al. found decreased activation in the left rostral supplementary motor area in hallucinating schizophrenic patients when they were requested to imagine words spoken in another person's voice. This task involved both the generation and monitoring of internal verbal activity. McGuire et al. concluded that the decreased activation in the supplementary motor area served as a neural basis of deficient self-monitoring in these patients. Therefore, it is possible that in the word list recall task of Dr. Crespo-Facorro et al. (1), the underactivation of the supplementary motor area was related to impairment of the self-monitoring of inner speech. However, on the basis of published data, this question remains unresolved. It would be interesting to know whether their patient group included hallucinating schizophrenic subjects and, if so, how their brain activation patterns differed from those of nonhallucinating patients. Moreover, it could be that during retrieval, the patients imagined the words being said in the experimenter's voice (the list was read to the subjects immediately before scanning) (1). These questions are important since, to our knowledge, independent research groups have not yet replicated the original findings of McGuire et al. (3).

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Dr. Crespo-Facorro and Colleagues Reply

TO THE EDITOR: We thank Drs. Kéri and Janka for their thoughtful comments about our recent PET study. Among other findings, we reported that compared to healthy volunteers, patients with schizophrenia showed a relative decrease in regional cerebral blood flow (rCBF) in the left rostral supplementary motor area when they recalled a practiced word list. Drawing from the findings of McGuire et al., Drs. Kéri and Janka suggest that the presence of hallucinating patients in our study group could explain the underactivation of the supplementary motor area. However, only five of 14 patients in our study had a clear history of auditory hallucinations (hearing voices commenting or conversing). Therefore, the majority of patients in our group were not hallucinators. This study was not designed to compare hallucinating and nonhallucinating patients.

Moreover, the cognitive paradigm in our study was not a task involving the generation and monitoring of inner speech. However, even if we assumed that the patients were performing some monitoring of their inner speech, similar rCBF decreases in the supplementary motor area would have been shown during the novel as well as the practiced conditions.

It is difficult to be certain whether patients do or do not experience auditory hallucinations during the performance of brief cognitive tasks in a PET session. We debrief patients and question them about the occurrence of auditory hallucinations after each injection. In our experience, patients rarely hallucinate when performing a cognitive task (e.g., remembering a list of words), especially when behavioral data confirm the task execution. Therefore, we think it unlikely that the relative decrease in rCBF in the supplementary motor area is associated with either the presence of hallucinators in our group or with hallucinations concurrent with scanning.

We and other groups have reported—albeit using different terminology and somewhat different concepts—converging results on the neuroanatomic substrates underlying the pathophysiological mechanisms of schizophrenia (1). The pre-supplementary motor area is involved in the internal representation of time and is activated during complex response-selection tasks (2). Reduced supplementary motor area activity has been associated with the impairment of self-generated willed actions (negative symptoms) and impairment of the self-monitoring of inner speech (positive symptoms versus auditory hallucinations) in schizophrenia (see Drs. Kéri and Janka's letter). The pre-supplementary motor area is connected to brain regions extensively related to the pathophysiological mechanisms of schizophrenia, such as the

prefrontal cortex, nucleus medialis, dorsalis of the thalamus, caudate nucleus, and cerebellum.

The "cognitive dysmetria" model of schizophrenia posits that a disruption in the normal coordination and sequence of mental processes may lead to a dysfunction in a fundamental cognitive process that defines the phenotype of the illness. Abnormalities in the circuit linking the brain regions involved in timing and sequencing mental functions (i.e., the cerebellum and pre-supplementary motor area) to regions involved in higher-level cognitive processes (i.e., frontal and parietal regions) might lead to this core cognitive impairment (3).

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Sympathoadrenal Hyperactivity and Neuroleptic Malignant Syndrome

TO THE EDITOR: The special article on sympathoadrenal hyperactivity and the etiology of neuroleptic malignant syndrome by Ronald J. Gurrera, M.D. (1), was enlightening. Although meticulously written and generously referenced, the article raises some interesting issues that we address here.

First, Dr. Gurrera drew attention to the fact that dopamine antagonism may not be essential for hyperthermia in neuroleptic malignant syndrome. This is based on a few anecdotal reports, which the author cites for support. However, how frequently does one encounter cases of neuroleptic malignant syndrome with hypothermia or neuroleptic malignant syndrome after a dose reduction or a discontinuation of antipsychotics? Furthermore, on the basis of this presumably unclear role of dopamine antagonism in hyperthermia, Dr. Gurrera mentions that in neuroleptic malignant syndrome, additional state-dependent factors are important mediators of dopamine antagonist effects, but he does not specify what these factors are.

Second, Dr. Gurrera mentions that the frontal lobes control sympathetic activity through the hypothalamus. However, through what mechanisms or neurotransmitters the frontal lobes effect this control requires clarification.

Third, the article delves into details on dopamine antagonism at the level of the spinal cord, which leads to sympathetic hyperactivity and the consequent emergence of the clinical features of neuroleptic malignant syndrome. However, dopamine antagonism at the level of the brain is meted out as just a passing reference. This engenders critical attention because the antipsychotic effect of neuroleptics is due to dopamine antagonism at the level of the brain and not at the level of the spinal cord. Is one to infer from this that patients prone to developing neuroleptic malignant syndrome have a variable sensitivity to dopamine blockade at different levels of the nervous system?

Fourth, does Dr. Gurrera purport to explain the altered sensorium so characteristic of neuroleptic malignant syndrome by disturbances in the neurotransmitters of the spinal cord? Emotional and psychological stresses associated with sympathetic hyperactivity appear a less convincing explanation for this altered sensorium.

Fifth, catatonia is stated to bear a strong resemblance to neuroleptic malignant syndrome, but no mention is made of γ-aminobutyric acid (GABA) in the pathophysiology of neuroleptic malignant syndrome. GABA has been implicated in catatonia; so have the frontal lobes (2). Does GABA play a part in the frontal inhibition of sympathetic drive?

Finally, the article mentions that alternative hypotheses of neuroleptic malignant syndrome do not enable clinicians to make reliable treatment choices. But does this hypothesis make things any better? After learning of Dr. Gurrera's strong bias for pinpointing peripheral sympathetic hyperactivity as being responsible for neuroleptic malignant syndrome, are we to believe that drugs blocking peripheral sympathetic receptors are a potential treatment modality for neuroleptic malignant syndrome?

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Dr. Gurrera Replies

TO THE EDITOR: The issues raised by Drs. Duggal and Nizamie are too numerous and diffuse to address within the limitations of a letter, so I will direct my remarks to the principal focal point of their commentary, which concerns the role of dopamine antagonism in the pathophysiology of neuroleptic malignant syndrome.

First, Drs. Duggal and Nizamie are unimpressed by the data linking hypothermia to dopamine antagonism and wonder (if only rhetorically) why hypothermia is not observed more frequently in neuroleptic malignant syndrome. A good deal of controversy in the literature of neuroleptic malignant syndrome centers on which clinical features ought to be considered essential for diagnosis; hyperthermia—the most dramatic and prognostically important sign—is usually accorded this status. This prevailing view has almost certainly reduced the likelihood that any episode resembling neuroleptic malignant syndrome that involves normal or subnormal body temperatures will be recognized or reported. Without intending to, Drs. Duggal and Nizamie have asked an incisive question, which I attempted to answer by reexamining our original database (1).

Of the 65 suspected episodes of neuroleptic malignant syndrome involving 45 patients, 22 episodes (33.8%)—involving 20 patients (44.4%)—had at least one subnormal body temperature nadir recorded within 7 days of the date that the episode reached maximal intensity. Nadirs (lowest temperatures recorded on any given day) ranged from 93.3°F to

98.2°F. Diaphoresis was observed in 11 (50%) of the episodes and more frequently in episodes with the lowest temperature nadirs, although this difference was not statistically significant (median split: 63.6% and 36.4%, respectively; Pearson's χ^2=1.64, df=1, p=0.20). Episodes with observed diaphoresis had a lower mean temperature nadir than episodes without observed diaphoresis, but once again this difference failed to reach statistical significance (95.8°F, SD=0.81; 96.7°F, SD=1.44, respectively) (p=0.13, n.s.). These data should be treated cautiously because temperatures were taken orally, so patients' inability to cooperate would tend to bias measurements toward lower temperatures. However, these data suggest that hypothermia may be more common in neuroleptic malignant syndrome than has been appreciated and that excessive diaphoresis may play a role. As Drs. Duggal and Nizamie imply, oscillations between hypo- and hyperthermia in neuroleptic malignant syndrome would be consistent with the model that I have proposed.

Second, they disapprove of the emphasis given in that model to dopaminergic modulation of sympathetic activity at the level of the spinal cord, but in support of their view they offer only a dogmatic assertion that the "antipsychotic effect of neuroleptics is due to dopamine antagonism at the level of brain and not at the level of spinal cord." I am unaware of any data that would validate this arbitrary distinction, and it seems premature to exclude involvement of the lower central and/or peripheral nervous system from the phenomenology of psychotic disorders.

In any event, Drs. Duggal and Nizamie have misconstrued one of the main points of my article, which is that whatever contribution is made by antagonism of the hypothalamic dopamine receptors to the pathophysiology of neuroleptic malignant syndrome, it is insufficient in itself to account for most of the observed clinical phenomena.

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