Simultaneous True Seizures and Pseudoseizures

Sir: Pseudoseizures may often occur in patients with epilepsy. We describe a patient in whom true seizures and pseudoseizures always occurred together.

Case report: Ms. A, a 45-year-old woman, was referred with a 3- to 4-year history of pseudoseizures. The events occurred 6 to 10 times a year, almost always started when Ms. A was in the company of others, and comprised wild, bilateral thrashing of the limbs, convoluted movements of the trunk, crying, resistance of assistance, rolling on the floor, and other bizarre phenomena. Consciousness was fully preserved throughout each event, and recall of experiences during each event was intact. Each event lasted about 5 minutes and was followed by fatigue. All clinicians whom she had previously consulted had unhesitatingly diagnosed a conversion disorder and had attempted psychological treatment along conventional lines; their diagnosis was supported by the identification of issues related to stress and failure in coping.

Each event started in her left hand and was almost always followed by gradual slumping to the ground and the bizarre behaviors described above; on careful history taking, we found that whereas the phenomena on the right side of her body were random, those on the left side appeared to follow a pattern. Rhythmic, uniplanar jerks began in her left hand and spread to her left forearm and arm and then to her left lower limb; upon recovery, the transient weakness that she experienced was always greater on the left than on the right side.

Her residence was close to that of one of the authors (C.A.); accordingly, an arrangement was made that he be informed immediately of an event. The author was notified once the next event began and visited Ms. A’s residence. At the time of the visit, the event had concluded; however, examination revealed grade 3 to grade 4 power and absent deep tendon reflexes on the left side; findings were normal on the right. Reexamination an hour later found no abnormalities on either side.

A diagnosis was made of left-sided jacksonian seizures with the remaining manifestations identified as pseudoseizure phenomena. She was referred for neurologic evaluation. Further contact was lost because she preferred to be evaluated in her city of birth.

The classical progression characteristic of jacksonian seizures, the unilateral absence of deep tendon reflexes immediately after the seizure, and the return of reflexes an hour after the episode all confirm that our patient experienced genuine seizures in the left half of her body. What of the bizarre phenomena on the right side? Bizarre behavior is known to be associated with epileptic foci in limbic structures such as the temporal cortex and the anterior/basal frontal cortex. Nevertheless, for several reasons we believe that these phenomena were nonepileptic. Sensorium was completely preserved; this is not possible in a complex partial seizure or a seizure that has generalized. Jacksonian seizures arise in the primary motor cortex, and the limbic structures in the temporal and anterior/basal frontal cortices are anatomically too remote to be involved in a primary spread of seizure discharges. Finally, it is very unlikely that there were 2 independent seizure foci that always discharged simultaneously, causing jacksonian seizures and bizarre behavior as independent seizure phenomena. Despite the lack of an electroencephalogram, the absence of a video recording of the ictal phenomena, and the lack of follow-up, we believe that these arguments are sufficiently cogent for a positive diagnosis of true seizures simultaneous with pseudoseizures.

True seizures immediately followed by pseudoseizures are known in literature across situations, conversion phenomena should be differentiated from behavioral changes resulting from postictal confusion. Simultaneous true seizures and pseudoseizures, however, have rarely been described. In the only report that we identified, Devinsky and Gordon described 2 patients in whom nonepileptic behavioral changes were simultaneous with partial seizures.

In summary, clinicians should keep in mind that patients with pseudoseizures may experience true seizures in between episodes of pseudoseizures, true seizures immediately preceding episodes of pseudoseizures, or true seizures simultaneous with the pseudoseizures.

Drs. Andrade, Singh, and Bhakta report no financial or other affiliation relevant to the subject of this letter.

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The Emergence of Darkness Phobia in a Bipolar Patient During Quetiapine Treatment

Sir: Worsening or emergence of anxiety symptoms induced by atypical antipsychotics has been reported in the literature, especially obsessive-compulsive symptoms. Most of these cases have been described in schizophrenic patients. It is unclear how treatment with atypical antipsychotics may induce these symptoms, although a secondary serotonergic and dopaminergic dysfunction has been hypothesized.

To our knowledge, this is the first reported case of the emergence of simple phobia in a bipolar patient after the initiation of quetiapine treatment, which disappeared with the interruption of the medication.

Case report. Ms. A, a 34-year-old woman with a personal history of psoriasis and bipolar I disorder, was admitted to our hospital presenting with a manic episode with psychotic symptoms (DSM-IV-TR criteria). One year before, she had been admitted to another hospital for her first manic episode and began treatment with risperidone 6 mg/day. During that first hospital admission, she experienced severe extrapyramidal symptoms (EPS), and some weeks afterward she became depressed and hopeless and described catastrophic delusional ideas. After lithium (1200 mg/day) and venlafaxine (300 mg/day) were added and risperidone was tapered progressively, she recovered.

The Classical Progression Characteristic of Jacksonian Seizures
In May 2005, she presented, to our hospital, with her second manic episode with psychotic symptoms, and we decided to prescribe quetiapine to treat mania and prevent EPS. Three weeks before the admission, her mood became elevated, expansive, and sometimes irritable; she had insomnia; and she was hyperactive. During the week preceding admission, she had delusional thoughts about religious and mystic tasks to do in order to help people. She reported that she had disordered conduct and a significant D2 antagonism at higher doses of antipsychotic. She described the symptoms as egodystonic and irrational; she was aware of the darkness, needed to touch someone while she went to sleep, and was unable to walk in darkness alone. She described the symptoms as egodystonic and irrational thoughts, and she rejected the notion that delusional ideation might explain these symptoms. She had no other phobic or anxiety symptoms. We began psychotherapy (cognitive-behavioral therapy) to try to avoid any treatment with antidepressants, but the simple phobia symptoms continued. During the next 8 months, the dosage of quetiapine was decreased, although progressively and slowly to maintain the remission of manic symptoms. The phobic symptoms began to diminish after the dosage of quetiapine had been decreased to 400 mg/day, and they disappeared altogether after quetiapine treatment was stopped. Now, 6 months later, she is taking only lithium; she is euthymic and has no phobic or anxiety symptoms.

Anxiety disorder comorbidity rates vary between 30% and 60% in bipolar disorder. Bristol JH. Haloperidol and phobias [letter]. Am J Psychiatry 1982;139:1372–1374. The emergence of social phobia during clozapine treatment and its response to fluoxetine augmentation. J Clin Psychiatry 1999;60:819–823. The paradox of quetiapine in rapid cycling bipolar disorder. Bipolar Disord 2002;4:335–340. The exact mechanism for this bidirectional effect of atypical antipsychotics is unclear. It is reported that the serotonin-2 (5-HT2)/dopamine-2 (D2) antagonism of atypical antipsychotics is 30 mg/day. However, as gleaned from the past with haloperidol, there is a risk for potential relapse of the phobic symptoms to be unethical with the high dose of quetiapine that was necessary to achieve remission of the manic state.


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High-Dose Aripiprazole in Treatment-Resistant Schizophrenia

Sf: Aripiprazole, a dopamine-serotonin system stabilizer, is the latest addition to the armamentarium of antipsychotics. The maximum recommended dose for aripiprazole per the Physicians’ Desk Reference is 30 mg/day. However, as gleaned from recent reports, other atypical antipsychotics have been used in doses higher than those recommended by the U.S. Food and Drug Administration (FDA). Comparatively little information is available on the effects of high doses of aripiprazole in treatment-resistant schizophrenia.
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gested safety of aripiprazole at 75 mg/day. 2 Authors in a recent
crease and the clinical response make the above scenario less
manufacturer)1 and the temporal relation between the dose in-
tion that was carried out after a minimum interval of 2 weeks
long half-life of aripiprazole. However, an upward dose titra-
beyond 30 mg/day would have occurred even if the dose were
it could be argued that the improvement seen after dose titration
severity and side effects, are applicable to this case. In addition,
reports, including lack of objective assessment of symptom
zole was increased to 20 mg/day and then to 30 mg/day after
another 2 weeks. At 30 mg/day, Ms. A showed a partial
response (about 30% reduction in the hallucinations per her
self-report).

However, when no further improvement was seen during
the next 3 weeks, the dose of aripiprazole was then increased
after the patient agreed to an off-label trial beyond 30 mg/day;
the dosage was increased to 45 mg/day and, 3 weeks later, to
60 mg/day. At 60 mg/day, Ms. A’s symptoms showed about
75% reduction per her self-report. Her electrocardiogram
(ECG) showed no abnormalities throughout this titration. Fur-
thermore, she exhibited no metabolic side effects such as hy-
perglycemia and dyslipidemia.

Three weeks after the start of treatment with 60 mg/day of
aripiprazole, the dose was titrated up to 75 mg/day, and within
4 weeks of this increase, the hallucinations remitted completely
and marked improvement in biological symptoms and social
and academic functioning was seen. The only abnormality no-
ticed in her ECG at that point was sinus tachycardia (100–110
beats/minute). She was maintained on 75 mg/day of aripipra-
zole for the next 10 weeks (with sustained complete remission
of symptoms); no adverse symptoms, including extrapyramidal
symptoms (EPS), akathisia, nausea, vomiting, orthostatic hypo-
tension, seizure, and weight gain, were noticed. As this was
Ms. A’s first psychotic episode, aripiprazole was tapered and
subsequently stopped over the next 10 months with no relapse
of symptoms.

This case highlights the safe and effective use of high doses
of aripiprazole. However, limitations inherent in single case
reports, including lack of objective assessment of symptom
severity and side effects, are applicable to this case. In addition,
it could be argued that the improvement seen after dose titration
beyond 30 mg/day would have occurred even if the dose were
to have been kept unchanged at 30 mg/day, considering the
long half-life of aripiprazole. However, an upward dose titra-
tion that was carried out after a minimum interval of 2 weeks
(time needed to achieve steady state as recommended by the
manufacturer)1 and the temporal relation between the dose in-
crease and the clinical response make the above scenario less
likely.

A review, citing a poster of a pharmacokinetic study, sug-
gested safety of aripiprazole at 75 mg/day.7 Authors in a recent
report of an overdose on 330 mg of aripiprazole suggested that
aripiprazole’s therapeutic index is quite high and that the drug’s
partial agonist effects should, theoretically, prevent many of the
adverse effects associated with other antipsychotic medica-
tions.5 The latter is also suggested by the observation that even
at striatal D2 receptor occupancy above 90%, EPS were not
observed with aripiprazole treatment.4

In contrast, a review on the dose-response relationship of
atypical antipsychotics demonstrated that aripiprazole at
10 mg/day was fully efficacious.5 Nevertheless, in clinical prac-
tice some patients do respond to higher doses of quetiapine and
olanzapine, as borne out by recent literature.2,6 Whether this
finding extends to aripiprazole is worth exploring, considering
its unique mechanism of action.

Drs. Duggal and Mendhekar report no financial or other affiliation
relevant to the subject of this letter.

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Clozapine Augmentation With
Aripiprazole for Negative Symptoms

Sir: Clozapine has long been viewed as the gold standard
used for schizophrenia patients refractory to treatment with
typical and atypical antipsychotics. Although clozapine is high-
effective, a number of patients are also treatment refractory
or only partially responsive to clozapine. For these patients,
augmentation strategies can be considered after a careful evalua-
tion of risk versus benefit to avoid potential drug interactions.
Several reports have demonstrated the use of atypical antipsy-
chotics such as risperidone, olanzapine, and ziprasidone as aug-
mentation agents to clozapine.1–5

In our review of the literature using a MEDLINE search
(2000–2005; keywords: clozapine, aripiprazole, combination,
drug therapy), we found no published reports on the use of ari-
piprazole as an augmentation agent to clozapine. Rather, we
found 1 report that describes the use of clozapine augmentation
of aripiprazole.6 The purpose of our report differs from the
above in that we propose the use of aripiprazole as an augmen-
tation agent to patients partially responsive to clozapine. The 3
patients presented have a DSM-IV diagnosis of schizophrenia
or schizoaffective disorder. They have been treated with cloza-
pine for at least 1 year and have received aripiprazole to aug-
ment response to clozapine.

Case 1. Mr. A, a 32-year-old man, has a 10-year history of
schizoaffective disorder, depressed type, with multiple prior
psychiatric hospitalizations and a history of assault in the con-
text of psychotic delusions. Having been treated unsuccessfully
with adequate trials of olanzapine and risperidone in the past, as

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of late 2004, he had been treated for over a year with clozapine 300 mg p.o. daily for psychotic symptoms and sertraline 100 mg p.o. daily for depressive symptoms. The patient refused an increase of the clozapine dose after experiencing hypersalivation, which was effectively treated with a transdermal weekly patch of clonidine 0.2 mg/day. His blood clozapine levels have been consistently found to be in the 303- to 353-ng/mL range.

The patient demonstrated improvement in positive symptoms with clozapine treatment, but his negative symptoms of flattened affect, social withdrawal, and apathy continued to persist. Due to persistent negative symptoms, aripiprazole was added and titrated to 30 mg p.o. daily within 1 month. No adverse events were noted with the combined use of aripiprazole and clozapine. Blood clozapine levels remained stable after aripiprazole was added; the most recently obtained blood clozapine level (7 months after initiation of aripiprazole treatment) was 353 ng/mL.

After 1 month of combined treatment, the patient displayed a fuller affect and began to spontaneously interact with staff in a socially appropriate manner. Due to his improved social skills, he was granted a patient work position as a therapeutic activity assistant. He continues to demonstrate improved work skills and shows initiative in learning new tasks. No further adjustments were made to his medication regimen.

**Case 2.** Mr. B, a 61-year-old man with undifferentiated schizophrenia, has a long history of repeated admissions with unsuccessful adequate trials of haloperidol and risperidone. As of late 2003, he had been maintained for over 3 years on clozapine 400 mg p.o. daily, with blood clozapine levels consistently ranging from 426 to 712 ng/mL. The patient has tolerated clozapine well, without side effects.

Despite adequate response of positive symptoms, the patient continued to display negative symptoms of isolation, affective flattening, and lack of motivation. He had poor hygiene, needing prompting for his activities of daily living. He also appeared uncomfortable in groups and frequently left groups early. To address his prominent negative symptoms, aripiprazole was added as an augmentation strategy and titrated over 1 month to 30 mg daily. Blood clozapine levels remained unchanged; the most recently obtained blood clozapine level (5 months after initiation of aripiprazole treatment) was 581 ng/mL. The patient tolerated the combined use of clozapine and aripiprazole well, without noted adverse events.

After 1 month of combined treatment, the patient displayed a fuller affect and became more sociable with both staff and other patients. For example, he is now able to participate fully in groups and stays through the entire allotted group time. The patient’s hygiene has also greatly improved; he no longer requires prompting for his activities of daily living. He continues to be maintained on clozapine 400 mg p.o. daily and aripiprazole 30 mg daily.

**Case 3.** Mr. C, a 37-year-old man with chronic paranoid schizophrenia, major depressive disorder in remission, and borderline intellectual functioning, had multiple prior psychiatric hospitalizations and unsuccessful adequate trials of risperidone, olanzapine, and haloperidol. As of late 2004, the patient had been on clozapine 700 mg p.o. daily for over 5 years and had had blood levels of 250 to 400 ng/mL. He experienced hypersalivation from clozapine, which was effectively treated with a transdermal weekly patch of clonidine 0.2 mg/day. In addition to clozapine, the patient has been on haloperidol 5 mg p.o. daily for over 4 years as an augmentation strategy for positive symptoms. For treatment of depressive symptoms, the patient has been maintained on venlafaxine 200 mg p.o. daily for over a year.

Despite adequate clozapine dosing and levels, the patient continued to display prominent negative symptoms of social withdrawal, poverty of speech, poor eye contact, and apathy. To target these symptoms, the patient was started on aripiprazole 15 mg daily, and his dose was increased to 30 mg daily within 1 month. He tolerated the combined use of aripiprazole and clozapine well without adverse events. Blood clozapine levels remained stable; the most recently obtained level (5 months after initiation of aripiprazole treatment) was 257 ng/mL. After 1 month of combined treatment, the patient displayed a fuller affect and improved eye contact and became more sociable in the unit. His improved motivation enabled him to participate in a work program at the hospital reserved for the most stable patients, and he has successfully taken on new responsibilities as a custodial assistant. No further adjustments of his medication were required.

This report presents 3 cases of successful augmentation of clozapine with aripiprazole for treatment-refractory negative symptoms. The decrease in negative symptoms may be related to aripiprazole’s combined actions on serotonin and dopamine. As a potent dopamine D2 partial agonist, aripiprazole blocks D2 receptors under hyperdopaminergic conditions and acts as an agonist under hypodopaminergic conditions, thus stabilizing dopamine output. 1,3 The reduction of dopamine hyperactivity by clozapine may create a hypodopaminergic environment in which aripiprazole may act as a D2 agonist and decrease negative symptoms. These preliminary results need to be verified by a controlled randomized trial.

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Early Bicarbonate Loading and Dantrolene for Ziprasidone/Haloperidol–Induced Neuroleptic Malignant Syndrome

Sir: Neuroleptic malignant syndrome (NMS), when severe, is associated with a 10% mortality rate.1 Many patients exhibit renal dysfunction often due to myoglobinuric renal failure secondary to rhabdomyolysis.1 In one series of cases of severe NMS, over 50% progressed to renal failure.2 Randomized controlled trials of early and preventive alkalization with sodium bicarbonate have demonstrated protective effects in patients at risk for contrast-induced nephropathy,3 as well as protection against nephropathy in patients with early rhabdomyolysis, a variety of intoxication states, and acute ischemic renal failure in animal models.4 However, there are no reports of the renal effects of early urinary alkalization in patients with NMS.

Case report: Mr. A, an 18-year-old man with autism and intermittent explosive disorder (DSM-IV criteria), was admitted in 2005 from the group home in which he had been living for nearly 3 months for self-injurious behavior (e.g., head banging and face slapping) that had resulted in multiple facial lacerations.

He initially presented to the emergency department at an outside hospital, where he received two 20-mg intramuscular (IM) injections of ziprasidone over approximately 4 hours. Thereafter, he was transferred to our psychiatric emergency department, where he received an additional 2 injections of IM ziprasidone (20 mg each, 5.5 hours between doses) followed by IM lorazepam (2 mg), diphendydramine (50 mg), haloperidol (10 mg and 10 mg), and benzotropine (1 mg). He was admitted to the inpatient unit, where he required intermittent restraint and seclusion for safety due to agitation.

Approximately 12 hours after admission and 13 hours after his last dose of antipsychotic, he became diaphoretic, tachycardic (180 beats per minute), tachypneic (60 respirations per minute), and delirious. His rectal temperature was 103° F, and his physical examination was significant for increased muscle tone in all 4 extremities. Neurologically, he was unable to follow commands; had gag, corneal, and oculocephalic reflexes; and had myoclonus. A presumptive diagnosis of NMS was made, and intravenous (IV) dantrolene sodium (2 mg/kg) was ordered. Supplemental oxygen via a non-rebreather mask was administered, electrocardiographic monitoring that demonstrated sinus tachycardia was begun, and 2 large-bore IV catheters were placed. One ampule of sodium bicarbonate was given, and volume resuscitation was initiated with 1.5 L of normal saline. Over the next 30 minutes, 2 L of crystalloid each containing 2 ampules of sodium bicarbonate were infused along with dantrolene (2 mg/kg), and thereafter an arterial blood gas demonstrated a metabolic alkalosis (pH = 7.47) most likely related to the bicarbonate loading. At that time, hemogram findings demonstrated a white blood cell count of 15.2 (at admission, the count was 10.8) but was otherwise within normal limits, as were the findings of his serum electrolytes, liver enzymes, blood urea nitrogen (BUN)/creatinine, and coagulation studies.

Having received 250 mEq of sodium bicarbonate (five 50-mL ampules of 8.4% sodium bicarbonate solution) and 5 L of crystalloid with matched production of clear urine, he was transferred to the medical intensive care unit, where creatine kinase concentration and renal function were followed serially. His creatine kinase concentration peaked at 3515 mg/dL, but his creatinine and BUN levels never increased above 0.8 mg/dL and 8 mg/dL, respectively. After 1 day in the intensive care unit, he was transferred to the general medicine service and subsequently returned to the psychiatry service, where treatment with valproate (500 mg, twice daily) was begun. Four days later, he was discharged to his group home in good condition and at baseline level of function.

This case suggests that sodium bicarbonate loading with adequate hydration may have a renal-protective effect in NMS. However, we cannot directly link our patient’s clinical improvement with the bicarbonate loading. Nonetheless, studies of rhabdomyolysis in surgical patients suggest that patients with creatine kinase concentration > 5000 mg/dL (pre-resuscitation) were significantly more likely to have persistent renal failure and that this possibility dramatically increases with a base deficit ≥ 4, which existed in our patient and was corrected by bicarbonate loading. Moreover, the alkaline load given to our patient did not induce hypokalemia, nor did it produce any cardiac arrhythmia or clinically significant alkalosis. Given the relative safety, practicality, and low cost of bicarbonate loading with hydration, we suggest that this therapy may be considered early in the course of treatment for patients with NMS. However, future studies are needed to generalize this finding.

Dr. Keck is a consultant to or member of the scientific advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Eli Lilly, Ortho-McNeil, Pfizer, and Shire and is a principal investigator or coinvestigator on research studies sponsored by Abbott, the American Diabetes Association, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Janssen, Merck, National Institute of Mental Health, National Institute on Drug Abuse, Organon, Ortho-McNeil, Pfizer, the Stanley Medical Research Institute, and UCB Pharma. Dr. Strawn reports no financial or other relationship relevant to the subject of this letter. The authors thank Mr. Paul Fracis, P.A.-C., and the nursing staff of 8-West for their clinical assistance.

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