Thyroid Myopathy With Rhabdomyolysis Presenting as Agitation: A Case Report

Sir: Rhabdomyolysis, a syndrome characterized by muscle necrosis, can be fatal, and it needs immediate attention. It can be classified as either traumatic or nontraumatic.[1] Nontraumatic rhabdomyolysis is associated with many etiologies, including hypothyroidism.[2] In both traumatic and nontraumatic rhabdomyolysis, intracellular muscle contents are released into systemic circulation. There are a few reported cases of hypothyroidism disclosed by rhabdomyolysis.[2–6] We hereby report a rare case of a patient who presented with new-onset gait abnormalities, limb weakness, rhabdomyolysis, and agitation, which were precipitated by noncompliance with levothyroxine and were secondary to hypothyroidism. The noncompliance was secondary to the patient's paranoia. Since the patient carried the diagnosis of schizophrenia, his agitation was automatically and incorrectly attributed to his mental illness.

Case report. Mr. A, a 65-year-old white man, was admitted to the psychiatric intensive care unit (PICU) for psychomotor agitation and combative behavior in April 2007. He had a past medical history significant for hypothyroidism secondary to thyroidectomy and radical neck dissection for carcinoma. It was reported that, a few weeks before admission, Mr. A had been threatening his caregivers, shaking his fist, and raising his voice. In addition, 2 days prior to admission, he woke up unable to walk but able to crawl to a phone and seek help.

Mr. A's agitation was presumed to be a result of his mental illness. Due to his past psychiatric history of untreated schizophrenia, he was directly admitted to the PICU from the emergency room. The results of a complete blood count, basic metabolic profile, erythrocyte sedimentation rate, coagulation profile, magnesium and phosphate levels, liver function tests, urine drug screen, and routine urine analysis were normal. Mr. A's creatinine kinase (CK) level was elevated at 394 IU/L (normal range, 30–170 IU/L), with a CK-myocardial band isoenzyme fraction of 7.7, and his myoglobin level was elevated at 153 ng/mL. His troponin levels were normal. Thyroid-stimulating hormone (TSH) and thyroxine (T_4) levels were 60.4 mU/L and 2.9 mU/L, respectively. A head computed tomography scan revealed no definitive acute intracranial abnormality but was suggestive of chronic microvascular ischemic gliosis. A neurology consultation was sought for new-onset gait abnormalities and limb weakness. Mr. A refused to follow through with the consultant's recommendations of further neuroimaging, including a magnetic resonance imaging scan. His lower extremity weakness and gait instability were attributed to his profound hypothyroidism. The plan was to initiate levothyroxine along with physical therapy, but the patient did not agree to it.

Mr. A's CK level continued to elevate during his stay and peaked at 4969 IU/L on the fifth day after admission. Due to these high levels, he was transferred to the medical intensive care unit. Mr. A continued to be uncooperative with all of the interventions, including intravenous hydration. He was eventually transferred back to PICU on the same day. Mr. A continued to refuse psychotropic agents but accepted levothyroxine after much persuasion. In addition, he was treated with aggressive oral fluid resuscitation. With treatment, Mr. A's free T_4 and triiodothyronine levels normalized, and TSH levels were in a downward trend. Quite interestingly, his CK levels also normalized, and there was resolution of both his physical and psychiatric symptoms. This outcome provides evidence that hypothyroidism may account for rhabdomyolysis accompanied by psychiatric symptoms. Mr. A did not receive any neuroleptics for his aggression in view of elevated CK levels, and he refused to take valproic acid and lorazepam, which were recommended to address his impulsivity, irritability, and aggression.

Hypothyroidism may cause rhabdomyolysis and present with psychiatric symptoms, which may go unnoticed.[2–6] Mentally ill patients can have significant comorbid medical illnesses that may have a cause-effect relationship with the mental illnesses, as well. The agitation should not be automatically attributed to underlying psychiatric condition, and the necessary medical workup should not be withheld, as illustrated by this case report.

The authors report no financial or other relationship relevant to the subject of this letter.

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Hearing Hallucinations in a 12-Year-Old Child: Psychotic Disorders or Temporal Epilepsy?

Sir: Hallucinations are infrequently seen in prepubertal children. Differentiating psychotic disorders from hallucinations of organic origin is crucial.[1] Possible organic causes of hallucinations are temporal or frontal lobe epilepsies.[2–4] We here report the case of a child who presented with psychosis and nocturnal hallucinations and for whom temporal epilepsy was eventually diagnosed and successfully treated.

Case report. Patient A, a 12-year-old boy with no previous family or personal neurologic history, was referred to our child and adolescent psychiatric department at the University Hospital of Lille because of behavior disorders and nocturnal restlessness with hearing hallucinations and loss of urine. The nocturnal episodes posed the question of a hypothetical psychotic disorder.

In the first days following his admission, Patient A presented with anxiety disorders, impulsiveness, frustration intolerance, and auto- and hetero-aggressivity. He suffered from recurrent attacks of fear at night. The attacks started with a fearful scream for help; the boy appeared disoriented and did not respond properly. The attacks usually lasted for 20 minutes. During the attack, he regularly reported hearing voices, to which he listened attentively. Afterward, he regularly lost urine, and eventually he presented with amnesia of the attack.

Findings of a neurologic examination including routine and sleep-deprived electroencephalography (EEG) and cerebral magnetic resonance imaging were within normal limits.

During an exploration with nocturnal video-EEG, a panic-like disorder was recorded, starting at 11:00 p.m. during sleep and comprising the following signs: arousal, fearful scream, scared expression, extension and movement of arms, agitation with hetero-aggressivity, tonic posturing, and loss of urine. There was amnesia for the above-mentioned features of the attack. Five other short episodes occurred during the recording. The EEG showed rhythmic theta activity in the right central and right temporal regions.

The semiology of the attack and the EEG results were regarded as congruent with a right temporal epileptic seizure. An anticonvulsivant treatment with carbamazepine (40 mg/kg/day) and clobazam (10 mg/day) was started. Since then, no nocturnal seizures have been observed, and Patient A has exhibited less auto- and hetero-aggressiveness.

Hearing hallucinations are frequently seen in temporal and frontal epilepsy with other psychopathologic symptoms like psychomotor excitement, hostility, and suspiciousness.[2,3] Hebephrenic symptoms are often seen in frontal epilepsy. In temporal epilepsy, the seizures can be characterized by intense fear and complex hearing hallucinations. Consequently, it is often hard to distinguish temporal epileptic seizure from psychotic disorders.[4]

Patient A suffered from recurrent nocturnal attacks of fear characterized by unresponsiveness during the attacks, a stereotyped course of symptoms, and a short duration. Furthermore, the stereotyped content of his hearing hallucinations appeared to be congruent with an epileptic origin.

Patient A did not meet all DSM-IV[5] criteria for schizophrenia. The hearing hallucinations happened only at night, and he demonstrated no negative signs of schizophrenia.

Temporal epileptic seizures with hearing hallucinations and fear are often hard to distinguish from psychotic disorders, especially in the case of misleading circumstances. (Our patient presented with psychosocial and behavioral problems.) Scalp EEG is not always able to detect ictal activity, so additional video recording can help to uncover signs essential for differential diagnosis.

Appropriate explanation of the etiology and manifestation of temporal lobe seizures will also help educate patients and their families regarding the unusual behaviors that are part of this disorder and reassure them of the organic rather than psychiatric cause of the phenomena.

The authors report no financial or other relationship relevant to the subject of this letter.

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A Wellness Intervention Program for Patients With Mental Illness: Self-Reported Outcomes

Sir: Individuals with mental illness frequently have poor physical health, are overweight or obese, and have higher rates of hypertension, diabetes, respiratory disease, and cardiovascular disease, all of which may contribute to early mortality.[1–3] Persons with mental illness often experience weight gain and metabolic dysregulation during the course of their illness and treatment.[1,4,5] Effective management of persons with mental illness may require a holistic approach to care, one that includes not just their mental health but monitoring and improving their physical health as well.[6] This management could be provided in the primary care setting just as it is for the non–mentally ill population, including advice on smoking cessation, weight reduction, and exercise.

The Solutions for Wellness Personalized Program[7] is an ongoing 6-month lifestyle intervention program that was initiated in July 2001 for patients with mental illness living in the community. To increase awareness that community-dwelling individuals with mental illness will participate in wellness intervention programs to improve their health and well-being, we report outcomes from over 7000 program completers.

Method. Patients were provided program information and an enrollment form during a visit to their health care provider. In order to participate in the program, patients were not required to meet any criteria, such as DSM diagnosis, receipt of psychopharmacologic treatment, incident weight, or risk for weight gain. The decision to enroll was entirely up to the patient, and conduct of the program was independent of the health care provider, mental health center, or program sponsor. As part of the enrollment process, patients completed a questionnaire that included questions regarding diet, exercise, sleep, and stress management, which provided information for the development of

Table 1. Categorical Changes in Weight From Baseline in Program Completers and Noncompleters[a]

Follow-Up Survey	Completers, (N = 7836)					Noncompleters, (N = 29,412)				
	Weight Loss					Weight Loss				
	< 5 kg	5–7.5 kg	7.5–10 kg	> 10 kg	Weight Gain	< 5 kg	5–7.5 kg	7.5–10 kg	> 10 kg	Weight Gain
2	2860 (36.5)	828 (10.6)	228 (2.9)	728 (9.3)	2362 (30.1)	3523 (12.0)	1039 (3.5)	285 (1.0)	1097 (3.7)	3431 (11.7)
3	2128 (27.2)	913 (11.7)	312 (4.0)	1142 (14.6)	2006 (25.6)	1643 (5.6)	675 (2.3)	209 (0.7)	1015 (3.5)	1808 (6.1)
4	1857 (23.7)	892 (11.4)	362 (4.6)	1692 (21.6)	2082 (26.6)	963 (3.3)	450 (1.5)	159 (0.5)	903 (3.1)	1132 (3.8)
5	1690 (21.6)	836 (10.7)	364 (4.6)	2055 (26.2)	2041 (26.0)	407 (1.4)	212 (0.7)	76 (0.3)	582 (2.0)	565 (1.9)
6	1591 (20.3)	889 (11.3)	358 (4.6)	2467 (31.5)	2140 (27.3)	NA	NA	NA	NA	NA

[a]Values shown as N (% of total N). The numbers of participants in each weight-change category do not equal the total numbers for completers or noncompleters due to missing data on the follow-up surveys.
Abbreviation: NA = not available.

a personalized menu planner and exercise program. Participants signed an agreement at enrollment that allowed the use of non-identifiable data from the questionnaire and subsequent monthly follow-up surveys to be used to monitor program outcomes.

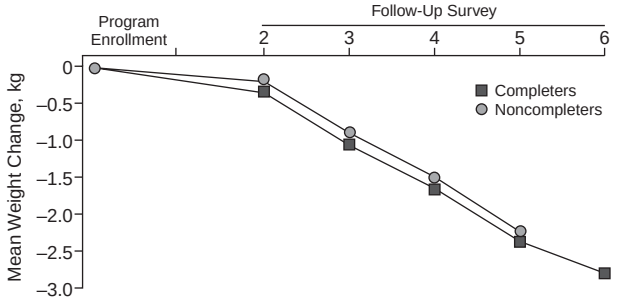
The results presented here were summarized from self-reported responses on follow-up surveys returned from July 1, 2002, through December 31, 2004. Participants who returned 5 follow-up surveys (surveys 2–6) were considered program completers; all others were considered noncompleters. Descriptive statistics (mean and standard deviation) were used to summarize data. Mean changes in weight and body mass index (BMI, kg/m^2) from enrollment to program completion were analyzed using last observation carried forward (LOCF), and monthly changes in weight and BMI were analyzed using observed cases. Differences between completers and noncompleters were evaluated using t tests at the 5% significance level.

Results. Over 5500 physicians across the United States referred patients to the program. Overall, most of the participants were women (84%) with an average age in their early 40s, and over 60% were obese (BMI > 30 kg/m^2). There were 7836 completers (21%) and 29,412 noncompleters (79%). The most common reason for enrolling in the program reported by completers and noncompleters, respectively, was the desire to improve their well-being (71.3% and 68.6%), although some indicated that they wanted to feel better about themselves (15.9% and 18.3%) and others wanted to improve their diet (6.3% and 6.5%) or fitness (6.5% and 6.6%).

At enrollment, program completers and noncompleters, respectively, reported that they were ready to improve their diet (98.8% and 99.0%), become more physically active (96.8% and 97.2%), sleep better (82.1% and 83.6%), and reduce stress (94.9% and 95.3%). On the second follow-up survey, completers and noncompleters reported that they were eating healthier (67% and 61%), had begun exercising (42% and 39%), had improved sleep habits (46% and 44%), and had reduced their levels of stress (57% and 55%). At the end of the program, over 90% of the completers reported that they had switched to healthier diets; over 80% had become more physically active, were sleeping better, and had less stress; and over 95% reported that they were confident in their ability to maintain these lifestyle changes. For the noncompleters, responses were summarized from their last available survey, which indicated that 85% had switched to healthier diets; over 70% were more physically active, were sleeping better, and had less stress; and over 90% were confident that they could continue with their changes in lifestyle.

BMI calculated from height and weight reported at enrollment indicated that 87% of completers and 86% of noncompleters were overweight or obese. The results from each follow-up survey for both completers and noncompleters indicated mean weight changes reflecting weight loss, although some participants gained weight (Table 1). Overall, the mean change in weight was –4.5 kg (–10.0 lb) for those participants who lost weight and the mean change in weight was +4.2 kg (9.3 lb) for those who gained weight. The mean weight change in program completers was –2.77 kg (–6.16 lb) with a corresponding mean change in BMI of –1.0 kg/m^2, and both of these changes were significantly greater than those reported by the noncompleters (–0.97 kg [–2.16 lb], $p < .001$; BMI of –0.35 kg/m^2, $p < .001$, LOCF). However, mean weight changes over time between completers and noncompleters were not significantly different in an observed case analysis (Figure 1). Among the overweight participants, the mean weight changes were –0.88 kg (–2.0 lb) for completers and –0.15 kg (–0.3 lb) for noncompleters. Among obese participants, mean weight changes were –4.1 kg (–9.1 lb) for completers and –1.5 kg (–3.3 lb) for noncompleters.

Figure 1. Mean Weight Change From Program Enrollment for Program Completers and Noncompleters



Self-reported outcomes from participants in this multifaceted wellness intervention program demonstrated that persons with mental illness living in the community can make lifestyle changes that improve their physical health and well-being. Most of the participants in this program were overweight or obese when they enrolled, and many of them reported having lost some weight, even those who did not complete the program. These results are similar to those from studies of commercial weight loss programs in nonpsychiatric overweight and obese subjects that reported weight loss in all participants, including those who discontinued early.[8,9]

Retention at the 6-month endpoint in this analysis was 21%, which is similar to findings in a naturalistic study of a commercial weight loss program that had enrolled over 60,000 clients and reported 22% retention at 26 weeks.[9] However, retention rates in open enrollment programs are considerably lower than those from randomized trials of weight management. In a yearlong study of 160 overweight or obese subjects who were randomized to 1 of 4 commercial diet programs, retention at 6 months was 62% and at 12 months was 58%.[8] In a 2-year trial[10] of overweight or obese subjects randomized to a commercial diet program (N = 211) or self-help group (N = 212), retention at 6 months was 83% and 81%. A 12-week clinical trial in overweight/obese persons with mental illness randomized to behavioral intervention or usual care reported a completion rate of 75%.[11] The higher retention rates in clinical trials may be due to the selective screening of potential participants and, perhaps, self-selection bias of successful participants.[10]

Attrition from weight-loss programs has been associated with age younger than 50 years,[12,13] depression/emotional difficulties,[13–15] smoking,[13] physical inactivity,[13] medical comorbidity,[13] and unrealistic weight goals.[16] The average age of the participants in this program was early 40s, and they were presumed to have a mental illness, were perhaps physically inactive, and may not have been ready to make lifestyle changes.[7] However, since the reason for participant dropout was not collected, it would be difficult to speculate which aspects of the program could be improved to increase completion rates.

Although program participation was associated with some weight loss and positive lifestyle changes, these results are greatly limited by the nature of their origin. Self-reported data from a loosely defined population constrain generalization, particularly to any diagnostic group of persons with mental illness. However, the positive results reported here are mirrored by similar findings reported by others for cohorts of persons with mental illness who participated in weight loss/lifestyle intervention programs.[17,18] Furthermore, the impact of lifestyle changes on dimensions of physical health is limited by the lack of clinical laboratory measures of glucose, cholesterol, and triglycerides, which define the metabolic state associated with being overweight or obese.

In conclusion, the overall long-term experience with the Solutions for Wellness Personalized Program demonstrates that persons with mental illness have the desire to improve their health and well-being. Physicians treating persons with mental illness should encourage them to participate in programs that provide education and support for lifestyle changes, which may help them achieve these goals.

Suppported by Eli Lilly and Company.

Drs. Hoffmann, Bushe, and Ahl and Mr. Meyers are employees and/or stockholders of Eli Lilly and Company, Indianapolis, Ind. Dr. Greenwood and Ms. Benzing are employees of Patient Marketing Group, Princeton, N.J., which is currently contracted by Eli Lilly and Company to implement this program.

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Panic Disorder After the End of Chronic Alcohol Abuse: A Report of 2 Cases

Sir: Comorbidity rates between alcoholism and panic disorder (PD) vary widely in several clinical trials.[1,2] Some trials reveal alcoholism rates in PD similar to those in the general population (between 14% and 16%),[3,4] and between 7% and 17% in agoraphobic patients,[5,6] whereas other studies find higher rates ranging from 20.7% to 28%.[7–9]

Some studies have suggested that individuals seeking treatment of alcohol use problems and dependence often meet diagnostic criteria for panic attacks, panic disorder, and agoraphobia.[10,11] Other investigations have indicated that persons seeking treatment of panic-related problems often meet diagnostic criteria for alcohol problems.[12] Otto et al.,[8] as one example, found that approximately 25% of persons seeking treatment for panic disorder had a history of alcohol dependence.

Panic attacks may be related to drinking aimed principally at reducing anxiety states and aversive bodily sensations. Yet such negative-affect–reduction drinking may, over time, have paradoxically anxiogenic effects by promoting heavier drinking, somatic dysregulation (e.g., recovery from heavy drinking episodes), and greater degrees of withdrawal symptoms. To the extent that individuals with panic attacks continue to drink heavily to escape or avoid such aversive alcohol-related internal states, they may be more likely to progress beyond heavy use and abuse to develop tolerance and withdrawal-related problems associated with alcohol dependence.[13]

Panic attacks, specifically, may be expected to developmentally precede alcohol use problems because recent investigations indicate that panic attacks may be a general risk marker for later substance use problems.[14]

Herein, we report 2 similar cases in which first panic attacks were experienced 1 month after abrupt cessation of alcohol abuse, indicating chronic alcohol use as a possible matter for development of panic disorder. Our cases, to the best of our knowledge, are the first in the literature in which panic disorder has developed after the cessation of chronic alcohol abuse.

Case 1. Mr. A, a 25-year-old barber, came to the psychiatry clinic with complaints consistent with a possible diagnosis of panic disorder according to the DSM-IV-TR criteria. Before he sought treatment at the clinic, he reported having up to 4 attacks per day, each lasting 1 to 2 hours on average and consisting of shortness of breath, chest pain, intermittently unreliable vision, nausea, diarrhea, and a sense of impending doom. For the most part, these symptoms appeared without warning, and over time he began to develop an intense underlying sense of anticipatory apprehension related to the unpredictable and uncontrollable appearance of these spells. Mr. A had had his first panic attack approximately 5 months earlier, 1 month after an abrupt cessation of an alcohol abuse period lasting 7 years. He had had almost no withdrawal symptoms except a feeling of dizziness that continued for 1 week.

Mr. A had been exhibiting antisocial behaviors, like frequent fights and incidents of shoplifting, since puberty, and he had a history of inhalant abuse between the ages of 17 and 20 years. During his sober times, Mr. A had realized that he was "a better man" (no fights, no arrests) and decided not to return to his "bad days." But he had started drinking again when the panic disorder symptoms made him "crazy." Three days after this restart, when he was arrested again because of a fight with the police, Mr. A made a definite decision to stop drinking, although alcohol had made his panic symptoms disappear completely. But the symptoms of panic attack had recurred after this decision, and he decided to see a psychiatrist. He reported no personal or family history of panic attacks. Mr. A was prescribed clomipramine 150 mg/day. The treatment has been helpful but his panic attacks have not entirely subsided with treatment.

Case 2. Mr. B, a 42-year-old automobile repairman, had a history of alcohol abuse for 16 years. He decided to stop drinking because of the unending insistence of his family and coworkers. He had had no withdrawal symptoms. However, approximately 1 month after the sudden cessation of alcohol abuse, he started to experience spontaneous episodes of panic attacks, with shortness of breath, chest pain, palpitations, trembling, and a fear that he was going to die. These attacks even interrupted his sleep; he would waken abruptly with a choking sensation. Two months after his first attack, Mr. B came for treatment, reporting a gradual increase in his symptoms that he related to his abrupt alcohol cessation. He stated that he would not drink again whatever happened but that he needed help for this new intolerable situation. He had no history of panic attacks before or during the alcohol abuse period. Mr. B was diagnosed with panic disorder according to the DSM-IV-TR criteria and was treated with paroxetine, initially 10 mg/day and gradually increased to 40 mg/day. He achieved remission of the panic attacks but was still presenting with limited symptom attacks related to stressful and threatening places or situations at 3 months' follow-up.

It is unclear whether panic attacks developmentally precede the onset of alcohol use problems or alcohol use problems precede the onset of panic attacks. The relative time to onset of the 2 disorders is a crucial issue that can shed light on etiopathogenic factors, in addition to having important practical implications. Clinical studies usually find that PD precedes alcoholism.[15,16] In addition, comorbid patients typically report that they use alcohol to relieve anxiety or panic symptoms.[17] In an experimental design, Kushner et al.[18] demonstrated that alcohol acutely reduced panic in patients with PD. These studies lend support to the self-medication (or tension-reduction) hypothesis, which states that patients with anxious disorders drink to relieve their symptoms of panic, thus developing alcohol problems. Alcoholism would then be secondary to PD.[19]

However, there is also clinical evidence that alcohol use, in addition to its initial anxiolytic effects, causes long-term increase in anxiety and agoraphobia.[15,20] A few clinical studies have also reported that alcoholism began before PD. In the Breier et al.[6] study, 80% of patients (8 of 10) had alcoholism before their first panic attack. The clinical study by Goldenberg et al.[21] failed to support the self-medication hypothesis. A reanalysis of the Epidemiologic Catchment Area study[22] found that, in subjects with comorbid alcoholism and PD, alcoholism appeared first in 60% of cases, and in 33% of individuals PD had an earlier onset.

Gender difference is also a confounding issue in the relationship between alcohol use and PD. In men, alcoholism was found to be primary with respect to PD (but not with respect to agoraphobia), whereas in women, alcohol problems were more frequently secondary to PD.[1]

Both Mr. A. and Mr. B had experienced their first panic attacks 1 month after abrupt cessation of alcohol abuse. They had no history of panic attacks during or immediately after the alcohol abuse period. Mr. A. had used alcohol to relieve his anxiety after the onset of panic disorder symptoms. Alcohol withdrawal in chronic alcohol use is reported to enhance noradrenergic

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activation and increase the likelihood of experiencing panic attacks in neurodevelopmentally vulnerable individuals. Alcohol has been hypothesized to have a kindling effect on the emergence of panic attacks.[23,24] Our cases may support this hypothesis; however, we do not consider panic disorder 1 month after the cessation of alcohol a withdrawal symptom.

Studies report an increase in anxiety and agoraphobia in alcoholic patients.[15,20] Although some experimental research indicates that alcohol reduces panic in patients affected from PD,[18] it is important to differentiate the short-term from the long-term effects of alcohol.

Although a short-term anxiolytic effect seems to validate the self-medication hypothesis, it is possible that alcohol use has a long-term panicogenic effect, particularly after cessation, as in our cases. Clinicians should be vigilant to psychiatric comorbidities in the patients who have alcohol use problems, especially in the abstinence period.

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Clozapine-Induced Stuttering: A Case Series

Sir: Stuttering is a condition in which the flow of speech or fluency is disrupted by involuntary speech motor events. The prevalence of stuttering in the general population is about 1%.[1] Stuttering may be developmental or acquired. Acquired neurogenic stuttering can appear for the first time in adulthood, and it is associated with a variety of temporary progressive and nonprogressive neurologic disorders, like traumatic brain injuries, strokes, extrapyramidal diseases, or use of certain drugs.[2] Drug-induced stuttering has been reported with psychotropic medications, including selective serotonin reuptake inhibitors,[3–5] tricyclic antidepressants,[6] phenothiazines,[7] olanzapine,[8,9] and clozapine.[10–14] We present a series of 3 patients who developed stuttering while taking clozapine.

Case 1. Mr. A, a 24-year-old man admitted in May 2007, was diagnosed with paranoid schizophrenia (DSM-IV).[15] He failed to respond to a 6-week trial of olanzapine 20 mg/day. He was started on clozapine, gradually titrated to 200 mg/day over 6 weeks. Mr. A responded to clozapine but developed stuttering at 200 mg, which stopped after clozapine was discontinued. His schizophrenia symptoms improved after 4 weeks of taking amisulpride 400 mg/day, with no recurrence of stuttering.

Case 2. Mr. B, a 35-year-old man, was admitted in May 2007 with schizotypal personality disorder (DSM-IV). He had frequent micropsychotic episodes, lasting for 2 to 4 hours, at least 3 times a day. These episodes interfered with his functioning significantly and necessitated the use of antipsychotics. He had received adequate trials of aripiprazole, flupenthixol, risperidone, and trifluoperazine. Mr. B developed truncal dystonia with trifluoperazine. He was subsequently started on clozapine treatment. At the time of consultation, he was taking 600 mg/day of clozapine. The duration of micropsychotic episodes reduced to 1 to 2 hours, and the frequency also reduced to once in 2 to 3 days with 600 mg of clozapine. In retrospect, the patient reported that stuttering started at 250 mg/day of clozapine and increased progressively with dose escalation. He did not manifest seizures at any time. Clozapine was gradually tapered over 2 weeks. Stuttering and micropsychotic episodes resolved with reduction in clozapine dose to 200 mg/day.

Case 3. Mr. C, a 23-year-old man, was hospitalized in June 2007 with a diagnosis of paranoid schizophrenia (DSM-IV). He had not responded to adequate trials of haloperidol and risperidone. He had developed tardive dyskinesia involving the tongue and upper extremities and nuchal dystonia prior to hospitalization. Clozapine was started in view of treatment resistance and involuntary movements. An electroencephalogram (EEG) taken before starting clozapine revealed no abnormalities.

Mr. C developed stuttering while he was taking 250 mg/day of clozapine. A second EEG revealed no abnormalities. The stuttering stopped after reducing the clozapine dose to 150 mg/day. Mr. C improved clinically at the same dose.

In all 3 patients, other causes of acquired stuttering were ruled out.

At the time of the first 2 case presentations, we were not aware of the association between stuttering and EEG abnormalities in patients taking clozapine. A literature search in PubMed using the keywords *clozapine* and *stuttering* showed 6 case reports.[10–14] Patients with stuttering have been found to manifest EEG abnormalities[16,17] that respond to anticonvulsant medication.[18] Stuttering has been considered a "minuscule convulsion."[19] Seizures and EEG abnormalities have been consistently associated with clozapine and are dose related.[20] Patients who developed stuttering while taking clozapine had EEG abnormalities and developed seizures.[12,13] Seizures associated with clozapine use have been reported to occur at doses higher than 600 mg per day,[12,13] and stuttering has been reported at doses between 400 to 700 mg/day.[10–14] Duggal et al.[13] report EEG abnormalities even before the onset of stuttering.

Available literature suggests that clozapine-induced stuttering may be a warning sign of impending seizures with preceding EEG changes. All of our patients developed stuttering at 200 to 250 mg/day of clozapine. Increasing the dose of clozapine did not precipitate seizures in any of our patients, nor was stuttering associated with EEG changes in the case of Mr. C. Decreasing the dose of clozapine resulted in resolution of stuttering in all patients. This finding shows that stuttering is clearly a dose-related side effect of clozapine. However, the relationship between clozapine-induced stuttering and seizures needs further investigation.

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