Gabapentin and Tiagabine for Social Anxiety: A Randomized, Double-Blind, Crossover Study of 8 Adults

Sir: Social anxiety disorder is characterized by fear and avoidance of social situations in which patients may feel scrutinized and considered foolish by others.[1] Social anxiety disorder can significantly impair educational, social, occupational, and physical functioning.[2]

Selective serotonin reuptake inhibitors have been the first line of treatment, but only a modest remission rate has been noted.[2] Selective serotonin reuptake inhibitors have gastrointestinal, activating, and sexual side effects that limit their utility. Benzodiazepines have been the second-line treatment for social anxiety disorder, mainly due to their potential for dependence and abuse.[3]

Two newer drugs, tiagabine and gabapentin, have been used in the treatment of anxiety disorders.[4–6] Tiagabine is a highly selective inhibitor of the γ-aminobutyric acid (GABA) transporter system (GAT-1).[4] Gabapentin is a mixed-type inhibitor of GABA transaminase.[7]

A small study was conducted at Eastern Virginia Medical School, Department of Psychiatry, in Norfolk, Va. from 2005 through 2007 after approval by the institutional review board that looked at the effectiveness of these 2 drugs in social anxiety disorder.

Method. Participants were 8 adults aged 21 to 39 years (mean, 26.5): 5 men and 6 white subjects, 1 black subject, and 1 Asian subject. Inclusion criteria were subjects who were aged 18 to 65 years, male or female, generally healthy, able to provide informed consent, and diagnosed with social anxiety disorder, which was confirmed by DSM-IV criteria and a Liebowitz Social Anxiety Scale (LSAS)[8] score greater than 30. Participants were excluded if they had another current Axis I psychiatric disorder, had a major medical illness, were taking medications that interacted with the study drugs, were actively using alcohol or illegal drugs, or were pregnant, planning to become pregnant, or breastfeeding.

The study was a randomized, double-blind, crossover design of 4 to 5 months' duration. Subjects had a washout period of 2 weeks if they were taking any medication for social anxiety disorder. They received a physical exam, a complete blood count, and a comprehensive metabolic panel. When patients successfully completed this phase, they were then randomly assigned to either tiagabine or gabapentin. Subjects had a 2-week titration to the full dosage of treatment arm A medication prior to a four-week stable dosage regimen. A 2-week washout period occurred between treatment arms. Treatment arm B included a 2-week titration and a 4-week stable dosage regimen. Patients were seen for a final visit 2 weeks after stopping study medication. The full daily doses were 2400 mg for tiagabine and 1800 mg for gabapentin. During each visit, the subject completed the LSAS, one of the most commonly used instruments for assessing social anxiety disorder.[9,10]

Results. Seven subjects had an initial LSAS score in the severe range, with 1 subject in the moderate range. All subjects with severe social anxiety disorder responded well to either anticonvulsant, with 2 subjects (1 for each study drug) reaching remission (LSAS < 30). On the LSAS total score, 4 subjects (2 receiving tiagabine and 2 receiving gabapentin) had clinically significant change (20 points). Patients reported very few side effects, with sedation and mild dizziness being the most common.

It appears that both gabapentin and tiagabine can be effective in reducing symptoms of social anxiety disorder as measured by the LSAS. Both medications were well tolerated, with only 1 person stopping gabapentin secondary to sedation. This small study adds to the existing database stating that the anticonvulsants gabapentin and tiagabine can be efficacious in the treatment of social anxiety disorder, with a favorable side effect profile compared to the selective serotonin reuptake inhibitor and benzodiazepine treatment choices.

Trial Registration: actr.org.au Identifier:12609000091202

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Dr. Spiegel has served on speakers or advisory boards for Pfizer, Astra-Zeneca, Janssen, and Bristol-Myers Squibb. Drs. Urbano, Laguerta, and Hategan and Ms. Shrader and Mr. Rowe report no additional financial or other relationships relevant to the subject of this letter.

REFERENCES

1. Mathew SJ, Ho S. Etiology and neurobiology of social anxiety disorder. J Clin Psychiatry 2006;67(suppl 12):9–13
2. Davidson JR. Pharmacotherapy of social anxiety disorder: what does the evidence tell us? J Clin Psychiatry 2006;67(suppl 12): 20–26
3. Keller MB. Social anxiety disorder clinical course and outcome: review of Harvard/Brown Anxiety Research Project (HARP) findings. J Clin Psychiatry 2006;67(suppl 12):14–19
4. Crane D. Tiagabine for the treatment of anxiety. Depress Anxiety 2003;18(1):51–52
5. Rosenthal M. Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control. J Clin Psychiatry 2003;64(10):1245–1249
6. Pande AC, Pollack MH, Crockatt J, et al. Placebo-controlled study of gabapentin treatment of panic disorder. J Clin Psychopharmacol 2000;20(4):467–471
7. Maneuf YP, Gonzalez MI, Sutton KS, et al. Cellular and molecular action of the putative GABA-mimetic, gabapentin. Cell Mol Life Sci 2003;60(4):742–750
8. Liebowitz MR. Social phobia. Mod Probl Pharmacopsychiatry 1987;22:141–173
9. Heimberg RG, Holaway RM. Examination of the known-groups validity of the Liebowitz Social Anxiety Scale. Depress Anxiety 2007;24(7):447–454
10. Sanjatovic M, Ramirez L. Rating Scales in Mental Health. 2nd ed. Cleveland, Ohio: Lexi-Comp; 2003

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Personality Disorder, Self-Mutilation, and Criminal Behavior

Sir: Self-mutilation and criminal behavior in people with personality disorder is not uncommon. It is a serious condition causing a lot of suffering not only to the individual but also for society in general. More work is needed in this area to improve the management of such patients.

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A 45-year-old single man with a repeated criminal history since age 14 years had a 12-year history of abusing drugs; several times, he seriously self-mutilated by cutting his abdomen when upset and resisting treatment thereafter. He was diagnosed with borderline personality disorder. Etiological factors and their implications on improving the management of such patients are discussed.

Case report. Mr. A is a 45-year-old single man who lives with his 82-year-old mother, selling firewood for a living. He has 3 brothers who have their own homes. His childhood was uneventful, although he stopped attending school at primary level after repeated truancies. His attitude toward his parents was defiant and rebellious; he stole from home on occasion and was disobedient to his parents. He never had a regular job.

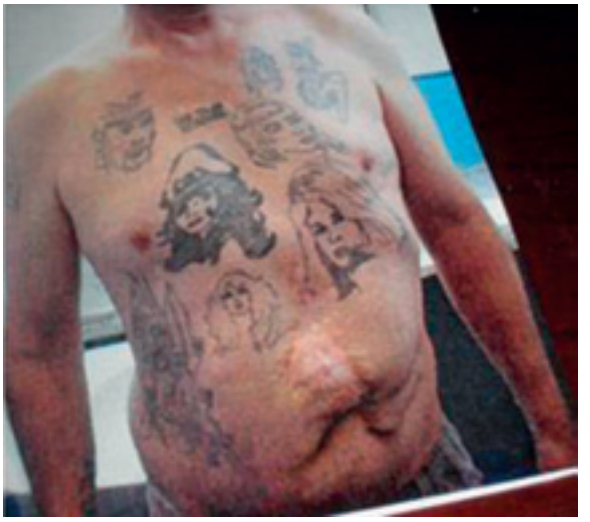
Mr. A has a long criminal history that began at the age of 14 years. Since then, he has been in and out prison numerous times, mostly for petty crimes such as disturbing public order. Once, he was charged with rape but was not convicted due to lack of enough evidence, and another time he was sentenced to 6 months in prison for a drug offense. He abused heroin and cocaine for 12 years. He spent a total of 19 years in prison for various offenses.

In December 2005, Mr. A was arrested again. The police report states that he hired a taxi and went to a house, where he threatened a female owner and took a television set by force. The taxi driver became suspicious that something unlawful was taking place, so he refused to take Mr. A to his desired destination and instead left him stranded. The taxi driver drove to the police station and reported the incident. Mr. A was later arrested and charged with burglary.

While in custody awaiting trial, Mr. A demanded to be immediately released or taken to court for a case hearing, claiming his innocence. Since he was not given either demand, he started a hunger strike, taking nothing except water. On the second day of food refusal, he took a razor blade and cut open his abdomen, attempting to put his hand inside the wound. He seemed not to be in pain. He even resisted help. Only after he was restrained was it possible to give aid and rush him to a general public hospital. The wound was cleaned and closed with 8 stitches. Antibiotics were prescribed, but he refused to take medication. He ended his hunger strike on the fourth day. After 3 days of hospitalization, he was brought back to prison. This time, he ripped open the wound and removed the stitches. There were signs of bacterial infection. He was pyretic (38.5°C) and his blood pressure was 120/90 mm Hg. Consequently, he was taken back to the hospital, where he stayed for 2 weeks before being transferred to another detention center. He did not self-mutilate or go on a hunger strike again until the court released him 4 months later. It was reported that 2 years before his present incarceration, he spent 10 months in prison and was released after cutting himself on the abdomen. He complained that no one took him seriously unless he cut himself. Medical records reveal that he has self-mutilated on several other occasions.

Mr. A at first refused to be interviewed with a mental state examination, but later changed his mind. In general appearance, he was unkempt and disheveled. He was anxious, restless, and agitated. He spoke with a loud voice. He did not have delusions or evidence of abnormal perceptions. His cognitive functions were intact. He had 5 large incision scars on his abdomen and tattoos on his chest, legs, and right arm (Figure 1). Physical examination results were basically within normal limits. A diagnosis of borderline personality disorder, subtype impulsive, was made according to DSM-IV.

Figure 1. Tattoos and Incision Scars on the Abdomen of a Self-Mutilating Case Subject With Borderline Personality Disorder



Mr. A had inappropriate intense anger, impulsivity, repeated self-destructive acts, and difficulty in establishing a relationship. He had a history of drug abuse, truancy, dropping out of school, unemployment, and many conflicts with the law. Self-mutilation is common in borderline personality disorder; usually, the patients' intent is not to end their lives.[1] The act could be one of a coping mechanism when, under severe stress, like a catharsis, they need to release emotions, distress, overwhelming feelings of anger, or emotional pain they cannot control.[2] Self-mutilation may be used as a form of communicating negative emotions. Mr. A has repeatedly cut deeply into his abdomen when upset. He removed stitches to stop the wound from healing. Before cutting himself, he expressed anger, aggression, and impulsivity. The cause of such destructive behavior is likely to be multifactorial, which may include psychological factors—a learned maladaptive behavior to get what he wants. Social factors may include interpersonal relationships, early childhood family environment, and childhood physical, sexual, or emotional trauma. Biological factors related to serotonergic dysfunction in the brain have been suggested.[3,4] There is a need for further studies in this area to determine the extent to which borderline personality disorder mood swings, impulsivity, aggression, anger, and self-harm are influenced by hereditary biological factors, particularly neurotransmitter disturbance. These factors may have significant implications in the treatment and management of borderline personality disorder patients.

Dr. Masala reports no financial or other relationship relevant to the subject of this letter.

REFERENCES

1. Oldham JM. Borderline personality disorder and suicidality. Am J Psychiatry 2006;163(1):20–26
2. Gunderson JG, Ridolfi ME. Borderline personality disorder: suicidality and self-mutilation. Ann N Y Acad Sci 2001;932:61–73; discussion 73–77

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3. Simeon D, Stanley B, Frances A, et al. Self-mutilation in personality disorders: psychological and biological correlates. Am J Psychiatry 1992;149(2):221–226
4. Ho MY, Al-Zahrani SS. 5-hydroxytryptamine and impulse control: prospects for a behavioral analysis. J Psychopharmacol 1998;12(1): 68–78

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A Case of Excessive Yawning With Citalopram

Sir: It has been identified but is not well-known or appreciated by practitioners that selective serotonin reuptake inhibitors (SSRIs) can cause excessive yawning as a side effect.

SSRIs are the treatment of choice for depression. The list of approved indications for these drugs has expanded to include obsessive-compulsive disorder, social anxiety disorder, generalized anxiety disorder, premenstrual dysphoric disorder, and eating disorders.

Gastrointestinal side effects, sexual dysfunction, and headache are the most common adverse effects seen with the use of these drugs. We report a case of a man who developed excessive yawning secondary to treatment with citalopram. A substantial amount of money was spent to treat his yawning before it was recognized that it could be a side effect of a medication.

Case report. Mr. A, a 58-year-old married white man with major depressive disorder, was admitted in December 2005 at the Comprehensive Epilepsy Center for electroencephalogram (EEG) monitoring to rule out epilepsy as a cause of excessive yawning. Mr. A's yawning spells had started several months previously and had become worse during the last couple of months. His estimated frequency of spells was 10 to 20 per day, with each spell lasting 10 to 30 minutes, and he would yawn 20 to 50 times per spell. Yawning spells would cause him to be lethargic, dizzy, and sometimes drowsy. These spells would come at any time and anywhere without warning. He found them distressing, embarrassing, and bothersome, so he decided to seek help from his primary physician, who did an initial evaluation and referred him to a neurologist to rule out a neurologic cause. Mr. A had had a transient ischemic attack a year before his December 2005 admission, from which he had fully recovered, and the neurologist recommended EEG, magnetic resonance imaging of the head with contrast, magnetic resonance angiography of the head, and Doppler studies of carotid arteries to rule out stroke, epilepsy, or tumor as a cause of excessive yawning. The results of all these studies were unremarkable. A cardiologist was also consulted to rule out a cardiac cause as the patient had a history of atrial fibrillation and 1 episode of chest pain. The cardiologist advised electrocardiogram, echocardiography, and angiography; these studies revealed no abnormality. Since this extensive workup could not point out the cause of the patient's excessive yawning, Mr. A was next referred to the epileptologist for EEG monitoring to rule out temporal lobe epilepsy.

Mr. A was admitted to the EEG monitoring suite for 5 days; continuous EEG monitoring and telemetry were performed, and prolactin levels were measured with each yawning spell. Electroencephalogram monitoring did not show epileptiform discharges, and prolactin levels stayed within normal range; telemetry showed sinus bradycardia ranging from 40 to 60 beats per minute with each spell. Complete blood cell count, comprehensive metabolic profile, international normalized ratio (INR), and urinary analysis results were also within normal range.

Table 1. Causes of Excessive Yawning

Epilepsy
Encephalitis
Brain tumors, stroke
Multiple sclerosis
Progressive supranuclear palsy
Opiate withdrawal
Heart attack, aortic dissection
Liver failure, renal failure
Drugs: selective serotonin reuptake inhibitors, clomipramine, desipramine, antiparkinsonism drugs

The medications he was taking at the time of admission were citalopram 20 mg/day for major depressive disorder, flecainide 50 mg every morning and 100 mg daily at bedtime for atrial fibrillation, and warfarin 5 mg/day. His depression was controlled well with citalopram, and atrial fibrillation was under control with flecainide. Mr. A denied using illicit drugs and admitted drinking socially.

On further questioning, the patient explained that his yawning began within 1 to 2 weeks of starting citalopram at 10 mg a day. It was not bothersome to him until 2 months previously when the dose of citalopram was increased to 20 mg/day for uncontrolled depression. His depression had responded well to the increased dose of citalopram, and he denied any daytime drowsiness.

During this hospitalization, epilepsy was ruled out, and extensive neurologic and cardiac workup ruled out other neurologic and cardiac causes of excessive yawning; normal test results for electrolytes, liver panel, and renal panel ruled out liver or renal disease.

SSRIs can rarely cause excessive yawning; thus, at the time of discharge from the hospital, we advised the patient to taper off citalopram gradually and to begin treatment with a non-SSRI antidepressant under the supervision of a psychiatrist.

After discharge, Mr. A tapered himself off citalopram treatment slowly over 2 weeks. With the weaning off of the dose of citalopram, his excessive yawning diminished and eventually stopped as citalopram was discontinued. Upon follow-up after 1 month of discontinuation of citalopram, Mr. A reported being free of excessive yawning. On further follow-up after 2 months, he continued to be free of excessive yawning, but his depression had relapsed. We followed up with the patient on the telephone 2 years after initial contact. He continued to be free from excessive yawning. He denied any depression at that time and had not taken any antidepressant in the interim.

Various causes of excessive yawning are presented in Table 1. In this case, the patient's excessive yawning occurred with the introduction of citalopram 10 mg/day but it was not bothersome to him until citalopram was increased to 20 mg/day; his excessive yawning remitted following discontinuation of citalopram.

Beale and Murphree[1] report 2 cases of excessive yawning with SSRIs. In the first, a patient was started on treatment with fluoxetine 10 mg/day for major depression, developed excessive yawning following 1 to 2 weeks of therapy, and remitted on discontinuation of fluoxetine; excessive yawning resumed following citalopram 10 mg/day initiation and stopped on discontinuation of citalopram. In the second case, a patient who was started on treatment with 50 mg/day sertraline for major

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depressive disorder also developed excessive yawning within 1 to 2 weeks after initiation of therapy, and his yawning remitted within 1 week of discontinuation of sertraline. In both cases, bupropion was started, and excessive yawning did not recur with bupropion therapy.

In a 6-week placebo-controlled trial using citalopram (N = 1,063) and placebo (N = 446), 2% of participants in the citalopram arm developed yawning, compared to < 1% of patients taking placebo.[4] In another study, 7% of patients with obsessive-compulsive disorder, 11% of patient with bulimia, and 1% of patients with panic disorder receiving fluoxetine reported yawning as a side effect of treatment, compared with 0% of patients receiving placebo.[4] In a study by McLean et al.,[2] clomipramine-induced yawning in humans was reported. In another study by Mogilnicka et al.,[3] yawning in rats treated with desipramine was documented. According to Goessler et al.,[5] the hypothalamus and hippocampus in the brain play an important role in yawning. Research has shown that yawning is largely affected by dopamine. Some other neurotransmitters involved are nitric oxide, serotonin, norepinephrine, acetylcholine, glutamate, γ-aminobutyric acid, oxytocin, and other neuropeptides; these have been shown to increase yawning when injected into the hypothalamus of animals.[5]

This case demonstrates that SSRIs can be associated with a bothersome side effect of excessive yawning, and this has been described in the literature with different SSRIs in varying incidences. If practitioners recognize this association, expensive and extensive workups may be prevented.

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

REFERENCES

1. Beale MD, Murphree TM. Excessive yawning and SSRI therapy. Int J Neuropsychopharmacol 2000;3(3):275–276
2. McLean JD, Forsythe RG, Kapkin IA. Unusual side effects of clomipramine associated with yawning. Can J Psychiatry 1983;28(7):569–570
3. Mogilnicka E, Wedzony K, Klimek V, et al. Desipramine induces yawning behavior in rats. Neuropharmacology 1986;25(7):783–786
4. Prozac (fluoxetine). Physicians' Desk Reference. Montvale, NJ: Thompson; 2006:1776
5. Goessler UR, Hein G, Sadick H, et al. Physiology, role, and neuropharmacology of yawning [in German]. Laryngorhinootologie 2005;84(5):345–351

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Treatment of Obsessive-Compulsive Disorder in a Mentally Challenged Adult: A Case Report

Sir: Obsessive-compulsive disorder (OCD) as a comorbidity was earlier considered to be very unusual among mentally retarded individuals.[1,2] However, current literature review reveals that OCD does occur at rates at least proportional to the general population but often remains undetected and untreated among individuals with developmental disabilities.[3] Herein, we describe the case of a patient with mild mental retardation and OCD, who responded to behavioral therapy.

Table 1. Assessment Scores of a Mentally Challenged Woman With OCD Treated With Escitalopram and Behavioral Therapy

Scale	Baseline	Week 4	Week 12
OCD severity scale[8]	27	18	11
CGI-I[9]	…	2	2
CGI-S[9]	5	3	2
Family Accommodation Scale[10]	30	16	7

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, OCD = obsessive-compulsive disorder.

Case report. Ms. A, an 18-year-old woman, presented to our hospital in November 2007 with an insidious onset, 6-month duration of illness characterized by repetitive acts such as cleaning; ritualized bathing, urination, and defecation; excessive need for symmetry in daily activities; and avoidance of morning duties. Nonperformance of proxy compulsions would make the patient aggressive.

A structured assessment was conducted at baseline and at subsequent follow-ups. The Mini-International Neuropsychiatric Interview,[4] Wechsler Adult Intelligence Scale-Performance Scale (Indian adaptation),[5] Yale-Brown Obsessive Compulsive Scale Symptom Checklist,[6,7] and a semi-structured clinical interview revealed that she had OCD, an intelligence quotient of 58 (mild mental retardation), contamination obsessions, and cleaning/washing compulsions. The details of the assessments are given in Table 1.

She was started on treatment with escitalopram 10 mg/day, which was increased to 20 mg over a period of 2 weeks. Differential positive reinforcement and performance-feedback procedures were initiated after family members were psychoeducated. By using differential positive reinforcement, exposure and response prevention was conducted. Initially, the patient received 20 sessions of inpatient behavior therapy on a daily basis and, later, 7 sessions on an outpatient basis.

Follow-up assessment at week 12 (see Table 1) revealed that Ms. A was mildly ill on the OCD severity rating scale and on the Clinical Global Impressions-Severity of Illness scale. The patient's parents also reported 90% improvement in her symptoms.

This patient with mild mental retardation and OCD responded to escitalopram and behavior therapy. The improvements attained at week 4 included a 33% decrease (based on a clinical significance formula[11]) in severity of symptoms; clinically significant reduction in proxy compulsions; and a 50% overall improvement of symptoms, which was reported by the patient's parents and was visible on the Clinical Global Impressions-Improvement scale. Another important issue that requires attention is the substantial decrease in OCD symptom severity and proxy compulsions, which occurred within the first 2 weeks of treatment. This improvement at week 4 (within the initial few weeks) would be attributed primarily to behavior therapy and not to serotonin reuptake inhibitor (SRI) medication, as it is well known that an SRI would take at least 8 weeks to demonstrate its benefits.

This case report assumes importance in the light of the paucity of studies reporting effectiveness of differential reinforcement procedures in causing clinically significant reduction in obsessional rituals in individuals with mental retardation. Physi-

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cians should keep in mind the effectiveness of differential reinforcement procedures in mildly mentally retarded patients who have OCD.

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

REFERENCES

1. Novosel S. Psychiatric disorder in adults admitted to a hospital for the mentally retarded. Br J Ment Subnormality 1984;30:54–58
2. McNally RJ, Ascher LM. Anxiety disorders in mentally retarded people. In: Michelson L, Ascher LM, eds. Anxiety and Stress Disorders: Cognitive-Behavioral Assessment and Treatment. New York, NY: Guilford Press; 1987:379–394
3. Wilson, SR. Identification and treatment of obsessive compulsive disorder in adults with developmental disabilities. Dissertation Abstracts International: Section B: The Sciences and Engineering, 2002, 63 (6-B) Jan: 3030
4. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
5. Swami PR. Indian adaptation of Wechsler Adult Intelligence Scale-Performance Scale: A Manual. Delhi, India: Manasayan; 1974
6. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, 1: development, use, and reliability. Arch Gen Psychiatry 1989;46(11):1006–1011
7. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, 2: validity. Arch Gen Psychiatry 1989;46(11):1012–1016
8. Vitiello B, Spreat S, Behar D. Obsessive compulsive disorder in mentally retarded patients. J Nerv Ment Dis 1989;177(4):232–236
9. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
10. Calvocoressi L, Lewis B, Harris M, et al. Family accommodation in obsessive compulsive disorder. Am J Psychiatry 1995;152(3): 441–443
11. Blanchard EB, Schwarz SP. Clinically significant changes in behavioral medicine. Behav Assess 1988;10:171–188

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Partial Seizures With Secondary Generalization While on Treatment With Clozapine and Sertraline: A Case Report

Sir: Clozapine is known to cause generalized and myoclonic seizures. Here we report a neurologically normal individual who developed partial seizures with secondary generalization while receiving clozapine and sertraline.

Case report. Mr. A, a 19-year-old man with paranoid schizophrenia whose psychotic symptoms had remitted with clozapine (300 mg/day), presented in 2007 with severe obsessive impulses to jump from heights. He had unremarkable birth and developmental history and had no past or family history of neurologic illness including epilepsy. He had never used psychoactive substances. His physical examination was normal. He was started on treatment with sertraline 50 mg/day, which was increased to 100 mg/day after 4 days; clozapine was continued at 300 mg/day.

A week after the sertraline dose was increased to 100 mg/day, his mother noticed twitching of the angle of his mouth, which deviated toward the left with jerky movements of facial muscles. This was followed, within seconds, by a generalized tonic-clonic seizure lasting for about 2 minutes. He regained consciousness after about 5 minutes. He was treated with intravenous phenytoin and subsequently (the next day) prescribed oral phenytoin (300 mg/day) and quetiapine (200 mg/day); clozapine and sertraline were discontinued. Magnetic resonance imaging (MRI) of the brain revealed no lesion that could explain focal seizures. Electroencephalograms (EEGs) recorded immediately following seizure and after 2 days were normal. He reported that he had involuntary twitching movements of his face toward the left starting on the day after sertraline treatment was begun. These lasted for a few seconds and occurred about 7 to 8 times a day, but he had not reported it until he had a generalized seizure.

Partial seizures decreased in frequency and stopped within a week; they did not recur while the patient was on treatment with quetiapine, which was built up to 800 mg/day over 2 weeks, along with phenytoin at 300 mg/day. Phenytoin was tapered and stopped after a 2-month seizure-free period. A diagnosis of seizure induced by combination of clozapine and sertraline was made.

This case illustrates that clozapine may cause partial seizures in neurologically normal patients. History, examination, and MRI revealed no neurologic problems. Seizures had not occurred while the patient was taking only 300 mg/day of clozapine but occurred immediately after adding sertraline. Sertraline can increase plasma clozapine level.[1,2] Since clozapine's epileptogenic property is dose dependent, this effect could induce seizures. Alternatively, sertraline could have independently put the patient at risk for development of seizures.[3]

About 10% of patients treated with any dose of clozapine develop seizures.[4] However, partial seizures due to atypical antipsychotics either have been associated with brain lesions[5–7] or have not been investigated for an association with such lesions.[7] We investigated our patient for possible focal lesions but could find none. Hypotheses that attempt to explain the epileptogenic properties of clozapine mainly apply to the generalized seizures.[7] One theory posits that clozapine increases rapid eye movement (REM) sleep and that a compensatory non-REM mechanism occurring during the wakeful state causes seizures. Another theory implicates mesolimbic selectivity of clozapine to explain its epileptogenic property.[7] Neither theory explains generation of partial seizures. The seizure threshold–lowering property of clozapine could have activated some micro-epileptogenic focus not detected by EEG and MRI in our patient. At this stage, this explanation remains hypothetical. Systematic analysis of EEGs and clinical seizures of clozapine-treated patients that looks specifically for evidence of the focal nature of the seizures may clarify whether clozapine can cause partial seizures in the absence of focal lesions.

Our patient did not complain of partial seizures until he developed a generalized seizure. It is possible that, in many patients, such partial seizures caused by clozapine could go unnoticed. It is tempting to hypothesize that partial seizures may be harbingers of generalized seizures in some patients, and if so, clinicians should have a high index of suspicion to look for partial seizures. Further research is needed to investigate this possible connection between partial and generalized seizures.

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

REFERENCES

1. Pinninti NR, de Leon J. Interaction of sertraline with clozapine [letter]. J Clin Psychopharmacol 1997;17(2):119–120
2. Centorrino F, Baldessarini RJ, Frankenburg FR, et al. Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. Am J Psychiatry 1996;153(6):820–822
3. Raju GV, Kumar TC, Khanna S. Seizures associated with sertraline [letter]. Can J Psychiatry 2000;45(5):491
4. Devinsky O, Honigfeld G, Patin J. Clozapine-related seizures. Neurology 1991;41(3):369–371
5. Pillmann F, Schlote K, Broich K, et al. Electroencephalogram alterations during treatment with olanzapine. Psychopharmacology (Berl) 2000;150(2):216–219
6. Wilson WH, Claussen AM. Seizures associated with clozapine treatment in a state hospital. J Clin Psychiatry 1994;55(5):184–188
7. Silvestri RC, Bromfield EB, Khoshbin S. Clozapine-induced seizures and EEG abnormalities in ambulatory psychiatric patients. Ann Pharmacother 1998;32(11):1147–1151

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Correction

In the ROUNDS IN THE GENERAL HOSPITAL offering "Multiple Neurologic, Psychiatric, and Endocrine Complaints in a Young Woman: A Case Discussion and Review of the Clinical Features and Management of Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke" by Chaya G. Bhuvaneswar, M.D., and colleagues (Prim Care Companion J Clin Psychiatry 2008; 10[3]:237–244), the second author's correct name is Jared M. Goetz.

The online version of the letter has been corrected.

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