Late Onset Neutropenia Associated With Clozapine

To the Editors:

Neutropenia and agranulocytosis (N/A) caused by clozapine are idiosyncratic, not dose-related reactions.[1] The exact mechanism of clozapine-associated N/A is unknown. It could be immune mediated or involve a toxic mechanism or even a combination of both. The disorder is reversible in most cases if clozapine is withdrawn promptly.[2] For patients on clozapine, the period of highest risk of N/A is during the first 6 to 18 weeks of treatment.[3] Nevertheless, it also has been reported that the risk for developing N/A endures for much longer periods.[3,4] There have been only 5 case reports of N/A at 5-year or longer treatment with clozapine.[5–9] However, in 3 of the 5 reported cases of late-onset N/A, the patients were taking additional psychotropic medications that carry a risk for blood dyscrasia,[10,11] namely, valproic acid, haloperidol, olanzapine, or risperidone. This raises the question of whether the N/A in those cases was truly clozapine associated or the result of synergistic effects on hematopoiesis, which led to an increased risk for N/A.

It has been suggested less frequent monitoring after 6 months of clozapine treatment especially in patients whose white blood cell (WBC) counts are consistently within normal limits, because of lower incidence of hematological risk (a rate probably no greater than that with many other drugs) after this period.[4] However, such approach might cause inadequate follow-up and also result in missing the prodromal period (a WBC <3500/mm^3; a large absolute drop in the WBC, even if the count remains >3500 mm^3; or 3 consecutive drops in the count), which might be a harbinger of agranulocytosis.[4]

We report a case of severe neutropenia associated with clozapine after 10 years of treatment (Fig. 1).

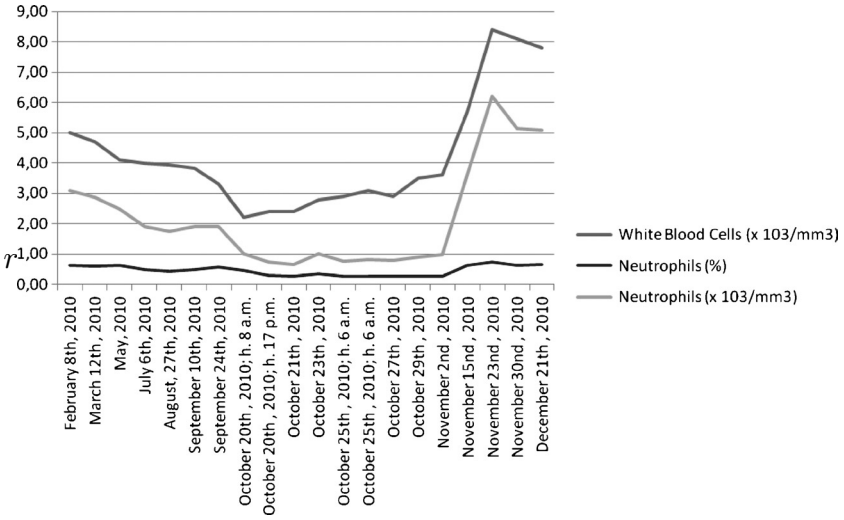

FIGURE 1. Late onset neutropenia associated with clozapine.

CASE REPORT

In 1991, we started clozapine treatment (150 mg t.i.d.) in a 55-year-old man affected by schizoaffective disorder, bipolar type (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*), who had been resistant to first-line antipsychotic treatment. During the first 9 years of treatment, hematological monitoring had always been normal. In May 2010, progressive neutropenia developed (Table 1). Before the start of neutropenia, no sign of infection had been observed, and no change in the brand of clozapine administered had occurred. On October 20, 2010, he was admitted to hospital for severe neutropenia and discontinuation of clozapine. Hematological monitoring confirmed worsening neutropenia (Table 1). Patient's psychiatric symptoms were in full remission. In the previous months, besides clozapine, he had initiated only metformin (250 mg b.i.d.) for diabetes mellitus, type 2. He also had assumed scopolamine, sporadically, for abdominal pain. In the course of hospitalization, a hematologist visited the patient and examined laboratory tests (including examination of blood smear) and did not find any other possible cause of neutropenia. The patient had no sign of infection. Routine laboratory tests were normal. HBsAg and hepatitis C virus tests were negative, Furthermore, iron, ferritin, transferrin, prealbumin, folate, vitamin B12, A-fetoprotein, carcinoembryonic antigen, CA 15, CA 125, CA 199, and prostate-specific antigen plasma levels were in the reference range. He was treated with risperidone (up to 6 mg/d) and then switched (for akathisia) to olanzapine 10 mg and quetiapine 150 mg at bed time. His clinical status remained stable and was discharged. Successive hematological monitoring confirmed progressive improvement and normalization of neutrophils blood count (Table 1).

DISCUSSION

In the present case, the etiological link between clozapine and neutropenia appears definite for three reasons: (1) lack of concurrent medical illness, (2) lack of concomitant drug treatment potentially associated with neutropenia (both metformin and scopolamine are free of hematological risks), and (3) remission of neutropenia after clozapine withdrawal. There seemed to be a trend of decline in WBC count for 7 months before the development of neutropenia that might have progressed into a state of agranulocytosis if no intervention had been conducted.

Gerson[12,13] postulated that clozapine can induce 2 distinct types of neutropenia: the first type is a mild-to-moderate neutropenia (neutrophil count below 1.5×10^9/L but not lower than 0.5×10^9/L), which occurs in 1.8% of treated patients. When clozapine is discontinued, recovery is rapid (2–8 days). The second type is more severe with a neutrophil count below 0.5×10^9/L and an incidence of 0.78%. In the second type, even if clozapine is stopped when the neutrophil count is just below 1.5×10^9/L, agranulocytosis none the less develops in some patients, usually within 2 to 5 days and generally lasting for 14 to 21 days. In such patients, monitoring allows the early detection and treatment but not the prevention of neutrophil suppression. The described patient seems to have experienced the second, more severe, type of neutropenia since remission occurred in nearly 1 month. In agreement with Tamam et al,[14]

TABLE 1. Late Onset Neutropenia Associated With Clozapine

Date	White Blood Cells ($\times 10^3/mm^3$)	Neutrophils (%)	Neutrophils ($\times 10^3/mm^3$)
February 8, 2010	5.00	62.9	3.1
March 12, 2010	4.70	60.4%	2.86
May 2010	4.1	61.1	2.50
July 6, 2010	4.00	47.7	1.91
August 27, 2010	3.94	44.2	1.74
September 10, 2010	3.84	49.4	1.90
September 24, 2010	3.30	56.8	1.90
October 20, 2010; h. 8 A.M.	2.20	45.4	1.00
October 20, 2010; h. 17 P.M.	2.40	30.2	0.73
October 21, 2010	2.40	26.6	0.65
October 23, 2010	2.80	36.0	1.01
October 25, 2010; h. 6 A.M.	2.90	26.4	0.75
October 25, 2010; h. 6 A.M.	3.10	26.5	0.82
October 27, 2010	2.90	27.8	0.80
October 29, 2010	3.50	26.0	0.91
November 2, 2010	3.60	27.6	0.98
November 15, 2010	5.70	61.9	3.60
November 23, 2010	8.40	73.6	6.20
November 30, 2010	8.10	63.7	5.13
December 21, 2010	7.80	66.0	5.10

we stress the need of stringent mandatory requirements for monthly blood monitoring in patients, given clozapine even after many years of treatment because it is the only way to prevent the risk of potentially fatal agranulocytosis.

AUTHOR DISCLOSURE INFORMATION

Dr Raja was on the speaker's bureau of Lundbeck and Chiesi Farmaceutici in the current year. The other authors declare no conflicts of interest.

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Delusional Parasitosis Associated With Donepezil

To the Editors:

In 1938, Ekbom described several cases of psychogenic parasitosis. He postulated that abnormal sensations and parasthesias lead to delusion formation in susceptible individuals.[1] Delusions of parasitosis, or delusional parasitosis (DP) as it also became known later, is commonly difficult to treat and usually commands multi-disciplinary approach.[1] We report a case of an abrupt onset of DP associated with donepezil use in an elderly patient with chronic diabetic neuropathy and poor visual acuity.

Mr B, an eccentric ex-couturier to the aristocracy, in his early 70s, described a 6-month history of pruritic infestation with insects. He recognized their complex life cycle from minuscule gray eggs buried under his skin that would hatch into silvery fish-like organisms with short legs. They would grow up to fingernail size and then crawl out of his nose, eyelids, teeth, and anus. During expectoration, some insects, in the end stage, would reinvade his digestive system and thus recommence this fictional cycle. His belief was resolute in its quality, rich in detail and flew in the face of numerous attempts by his family physician and his partner to prove its fallacy. Various laboratory investigations and the analysis of the samples of skin and excoriations, zealously brought in small plastic bags, excluded a true infestation (eg, scabies), primary systemic causes of pruritus and pediculosis.

His delusions revealed a close temporal association with a trial treatment with donepezil (5 mg daily) for a suspect mild vascular cognitive impairment. At some point, the dose was further inadvertently increased to 15 mg. The oversight was corrected, but he shortly started complaining of pruritus, burning pain, and

burrowing sensation over his body. Later examination revealed prurigo nodularis, lichen simplex chronicus, and numerous ulcers over parts of his neck, upper torso, and hands, presumed because of incessant scratching. No other hallucination or delusions were described.

Comorbidity included diabetic peripheral neuropathy with bilateral leg ulcers, cataracts, and osteoarthritis. Past history of depression, successfully treated syphilis, and intermittent alcohol abuse with liver cirrhosis also were recorded. Neuroimaging showed minimal patchy changes in the right subinsular white matter, suggestive of small vessel disease. He was otherwise neuropsychiatrically intact and scored 29/30 on Mini Mental Status Examination.

Delusional parasitosis was thought to be secondary to an interplay of a constellation of several organic conditions (eg, neuropathic pain, impaired vision, a potential disruption/dysfunction of right haptic striato-thalamo-parietal network) and putative neurochemical misbalance caused by donepezil. Donepezil was stopped, and quetiapine (25 mg daily) was prescribed. His delusions substantially declined over several weeks with complete resolution of the insect sensation after 4 months. Subsequent cessation of quetiapine did not lead to recurrence of delusional beliefs. Rechallenge with donepezil was not performed in view of uncertain benefits, potential risks, and patient's explicit wishes.

Although this is, to the best of our knowledge, the first report that potentially implicates donepezil in the genesis of DP, several other psychiatric adverse events were previously attributed to donepezil. Agitation was the most commonly reported psychiatric presentation in several clinical trials with donepezil, followed by anxiety and depression.[2] Rarer psychiatric presentations included mania, delirium, paranoid delusions, and hallucinations.[2–4] Increased somatic preoccupation and propensity for regression to earlier behavioral problems were also described in literature.[5]

Several lines of evidence suggest that dopaminergic neurotransmission plays the pivotal role in the etiology of DP.[1] Induction of DP by certain psychoactive agents is recognized, and hitherto, several iatrogenic drug-induced DPs also have been reported, tentatively implicating striatal dopaminergic dysfunction.[1] Acetylcholinesterase inhibitors (eg, donepezil) are believed to exert an indirect, complex, modulatory effect on nicotinic cholinergic receptors, speculatively resulting in both increase and decrease of striatal dopamine release.[6] Their judicial use is particularly advocated in elderly whose age-associated cholinergic loss and cumulative anticholinergic burden of polytherapy may all paradoxically conspire to initiate psychotic symptoms.

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Imipramine for Enuresis Associated With Risperidone

To the Editors:

Disruptive behavior disorders (DBDs) are often characterized by destructive behaviors, aggression, hyperactivity, impulsivity, low frustration tolerance, and temper tantrums. Risperidone has been reported to be effective in the management of DBDs. Although it is generally well tolerated, somnolence, rhinitis, headache, weight gain, and increased appetite are among the most reported side effects.[1]

Risperidone-related enuresis has been described as a relatively rare adverse effect.[2–4] However, Snyder et al[5] reported that 13.2 % of children with disruptive behaviors developed enuresis during risperidone treatment, which was 5.3 % in the placebo group. It is possible that occurrence of enuresis during pharmacotherapy may contribute to noncompliance and consequently decrease the quality of life of patients and their parents.

Here, we report a pediatric case that developed nocturnal enuresis during risperidone and was treated successfully after administration of imipramine. Patient consent was obtained from his parents for the treatment and publication.

CASE

A 12-year-old boy was referred to our outpatient clinic for his anger bursts, aggressiveness, and impulsivity. His IQ testing revealed borderline intelligence. Risperidone at 0.5 mg/d was initiated, but in the fourth day of treatment, he experienced nocturnal enuresis with a frequency of 4 to 5 times a week. As it did not resolve spontaneously, we ceased the medication in the fifth week. Two weeks later, we decided to restart risperidone owing to the severity of his disruptive behaviors, but his enuresis reemerged.

He had toilet training when he was 3 years old. His medical history and workup was unremarkable. He and his parents did not report any other adverse event during risperidone treatment. For his enuresis, behavioral intervention was initiated; however, no improvement was observed. Then imipramine, 25 mg at night, was added to the treatment regime; and after the first week, his enuretic symptoms resolved completely.

DISCUSSION

Development of enuresis after challenge, dechallenge, and rechallenge with risperidone and complete resolution after its discontinuation is suggestive of a causal effect. In addition, the Naranjo probability score[6] for adverse drug reactions was 9 points, indicating a "definite" relationship between risperidone and enuresis. However, the pathophysiology of enuresis associated with risperidone has not been well documented. The possible mechanisms include urinary retention and subsequent overflow incontinence due to antimuscarinic action and decreased internal urethral sphincter tone caused by α-1 adrenergic blockade effect.[4]

Antipsychotic-related incontinence is suggested to be time limited and does not require any therapeutic intervention; but in some cases, it does not resolve spontaneously as it was in this reported subject. Possible interventions to manage enuresis associated with antipsychotics include

cessation of the drug and, if indicated, restarting, prescription of the minimal effective dose, and switching to another antipsychotic drug with lower α-1 blockade effect.[3,4]

Several reports described effectiveness of adding several drugs to the treatment such as anticholinergics like oxybutynin[7] and trihexyphenidyl,[8] α-1 adrenergic agonists like ephedrine,[9] and desmopressin.[10] Recently, Praharaj and Arora reported efficacy of amitriptyline, a tricyclic antidepressant, on enuresis occurred during clozapine treatment.[11]

Imipramine, a tricyclic antidepressant, was found to be effective in the treatment of enuresis in children, but the exact mechanism of its action is unclear. It was suggested that the anticholinergic effect of the drug might result in a decrease in bladder contractility leading to increased bladder filling and improved functional bladder capacity.[12] Additionally, the therapeutic benefit may be due to its adrenergic effect by increasing urethral sphincter tone on the bladder trigone.[13]

This report suggests that in cases with enuresis that occurred during risperidone treatment, imipramine may be an alternative. More systemic studies are needed to determine the effects of imipramine on antipsychotic-related enuresis.

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Positive Impact of the β-Blocker Celiprolol on Panic, Anxiety, and Cardiovascular Parameters in Patients With Mitral Valve Prolapse Syndrome

To the Editors:

Mitral valve prolapse (MVP) is a pathologic condition that affects leaflet motion. Its frequency in the industrialized world amounts to 5% (women: men ratio = 2:1), mostly being a chance finding with a low complication rate of 2% p.a.[1] When MVP is associated with symptoms of panic, anxiety, fatigue, dyspnea, chest discomfort/pain, palpitations, and other autonomic symptoms (hyperadrenergic state), the constellation is termed *mitral valve prolapse syndrome* (MVPS). This condition resembles anxiety/panic disorder, and elevated blood levels of norepinephrine seem to play a role. During diagnostic workup, symptoms can be brought forward by isoproterenol during tilt test.[2] However, MVPS symptoms may not simply be explained by MVP. In terms of treatment, β-adrenoreceptor blockers are the gold standard, but by reducing heart rate (HR) and blood pressure (BP), they provoke adverse effects that overlap with the syndrome itself.[2] We hypothesized that symptoms of MVPS can be alleviated by celiprolol, a selective β-blocker with intrinsic sympathomimetic activity, namely, predominant β_1-adrenoceptor blockage with weak β_2-adrenoceptor stimulation. Theoretically, celiprolol may thus have a potential benefit on cardiac symptoms as well as on anxiety and panic without causing adverse effects. We expected (1) decrease in anxiety/panic and depression; (2) increase in tilt time, indicating a higher catecholamine tolerance; (3) no change in HR and BP; and (4) increase in exercise capacity.

Eleven patients (9 females, 2 males; aged 39.1 ± 14.8 years) with a diagnosis of panic and/or anxiety disorder made at the Department of Psychiatry and were sent for routine cardiologic workup to the Department of Cardiology, where the diagnosis of MVPS was established. Patients gave informed consent to participate in a prospective, consecutive cohort study approved by the local ethics committee. Patients presented with the following symptoms: panic (n = 7), tachycardia (n = 8), presyncope/syncope (n = 3), palpitations (n = 3), anxiety (n = 2), dizziness (n = 2), restlessness (n = 2), nausea (n = 1), and hyperventilation (n = 1). Following celiprolol treatment, fewer symptoms were reported: panic (n = 3), tachycardia (n = 4), presyncope/syncope (n = 4), palpitations (n = 1), anxiety (n = 1), and pulsation at the back of the head (n = 1); 2 patients were symptom-free.

Assessments on study intake and after a follow-up period of 30 days comprised medical and psychiatric history, cardiologic workup, and the Hospital Anxiety and Depression Scale-D (HADS-D; D = German version), which consists of the subscales anxiety (HADS-D/A) and depression (HADS-D/D), each comprising 7 items with a 4-level scale (0–3 points).[3] Celiprolol was administered orally and titrated from 100 to 200 mg/d.

Mitral valve prolapse was proven by color Doppler echocardiography (GE Vivid Five; Sanofi, Frankfurt, Germany) defined as systolic leaflet billowing of at least 2 mm below the CD-line in M-mode. Regurgitation was classified according to the respective guidelines.[4] Catecholamine tolerance was assessed with tilt-table testing. Following a 5-minute supine resting period, patients received isoproterenol infusion

1 μg/min (Isuprel; Sanofi Winthrop, Horten, Norway). Five minutes later, the tilt table was moved to an upright position (tilt angle: 60–70 degrees), with infusion flow-rate remaining unchanged. After another 5 minutes, isoproterenol dosage was increased up to a maximum of 5 μg/min, or until symptoms occurred, or until the maximum time (25 minutes) had elapsed. Patients also underwent bicycle spiroergometry, which allows the determination of oxygen consumption during exercise, an integrative parameter of the proper interplay of cardiovascular, pulmonary, and metabolic systems.

Statistical analyses were performed using SPSS (version 11.0; SPSS Inc, Chicago, Ill). Normal distribution was determined; data were log transformed if required, and between-group comparisons were performed by 1-way analyses of variance with Scheffé post hoc tests.

During the 30-day treatment period, anxiety levels significantly decreased from 10.3 ± 5.0 to 7.1 ± 3.7 ($P < 0.01$), that is, below threshold. Single patients' scores are depicted in Figure 1. The levels of depression were unremarkable throughout (4.9 ± 3.3 vs 3.9 ± 3.8; not statistically significant). On self-report, only 4 patients complained of panic or anxiety as opposed to 9 at study entry. The following diagnoses were established on follow-up: MVP in all patients, mitral valve regurgitation primary/secondary (1/1 patient), and billowing of 1 or both leaflets (6/5 patients). During the study period, catecholamine tolerance, that is, the cumulative tolerated dose of isoproterenol, significantly increased from 24 ± 14 μg to 62 ± 4 μg ($P < 0.001$) and tilt-test time from 12.3 ± 4.8 min to 21.1 ± 7.5 min ($P < 0.01$). Improved exercise capacity was indicated by slight decreases in both maximum HR at peak exercise (167.4 ± 20.7 per minute to 152.0 ± 16.4 per minute; not statistically significant) and maximum oxygen consumption (1.580 ± 238.7 mL to 1.414 ± 118.2 mL; not statistically significant). Patients' HR remained almost unchanged (73.0 ± 13.6 beats/min vs 72.0 ± 9.8 beats/min; not statistically significant) as did BP parameters (systolic: 120.2 ± 17.3 mm Hg vs 124.6 ± 14.3 mm Hg; not statistically significant; diastolic: 68.0 ± 10.9 mm Hg vs 68.5 ± 7.0 mm Hg; not statistically significant). In accordance with our hypotheses, MVPS patients benefited from treatment with celiprolol. They exhibited reductions of panic/anxiety and somatic MVPS symptoms, improved tilt testing, and negligible adverse effects, indicated by stable hemodynamics and exercise capacity.

Mitral valve prolapse syndrome patients usually experience exercise intolerance due to reduced central blood volume and abnormous venous return.[5] Their β-adrenoceptors are most likely hypersensitive and, compared with controls, easily become desensitized by isoproterenol.[2] Similarly, panic attacks may be produced by isoproterenol in panic patients only.[6] In the presented study, celiprolol significantly increased tilt-test time and the tolerated dosage of isoproterenol. Therefore, we reason that celiprolol may lead to an ameliorated catecholamine tolerance and thus differs from commonly used β-blockers.

In clinical practice, physiological symptoms of panic/anxiety and MVPS cannot be told apart, and on a scientific level, their relationship is not yet fully understood. A review by Margraf et al[7] on the topic included 17 studies on patients presenting with panic disorder or agoraphobia, 18% of whom also fulfilled criteria for MVPS as opposed to 1% in control subjects. Moreover, 8 studies on patients presenting with MVPS were reviewed, where the prevalence of incidental panic attacks was 14%. Other reviews[8,9] focused on different medical diseases that share comorbidities with panic disorder. The authors cite cardiac conditions such as MVP as representing a significant comorbidity. A meta-analysis on 21 studies found an increased relative risk for an association of MVP and panic disorder.[10] At least 4 different interrelations of MVPS and panic/anxiety disorder may be envisioned: (1) MVP may be based on physiological changes that are determined by panic disorder–related arousals with high levels of catecholamines. However, a relationship between catecholamines and panic/anxiety has not been established as clearly as in MVP. Moreover, continuously elevated HR, as associated with elevated catecholamines, is not a symptom of panic disorder. (2) Patients may experience panic on perception of MVP symptoms. As MVP mostly is a chance finding in the absence of symptoms, this argument is weak. (3) There may be a third factor underlying both disorders, for example, a distinctive autonomic feature. (4) Lastly, MVP and panic disorder may represent comorbidities.

In summary, the arguments do not favor a causal relationship of MVPS and panic disorder but rather a common underlying factor or a co-occurrence. An important question remains, namely, how both celiprolol and the β-adrenergic agonist isoproterenol may influence emotions. Both are hydrophilic agents and therefore may not pass the blood-brain barrier. Kielholz[11] postulated 3 mechanisms of β-blocker–related central actions: (1) indirect peripheral mechanisms by peripheral β-blockade and feedback; (2) direct specific actions through inhibition of central β-blockers; (3) direct unspecific actions, that is, central actions in the central nervous system (CNS) unrelated to adrenoceptor blockade. Obviously, in our case, the effects of both substances on panic/anxiety can be mediated only by peripheral adrenoceptors. This corroborates the hyperadrenergic state as the common pathway of MVPS and panic/anxiety leading to feedback via CNS circuits and to an adequate pharmacological effect following the application of β-blockers. Thus, a peripherally acting β-blocker may induce a negative feedback on CNS centers; that is, the vicious circle of anxious reactions to somatic symptoms may be interrupted.

It has to be critically remarked that our study lacks a control group. The patient sample is small but representative as age and sex distributions are comparable to the Framingham study.[1] However, because of the small sample size, conclusions on efficacy of celiprolol cannot be drawn. Other shortcomings are the lack of standardized psychiatric assessments and the "referral bias." Lastly, there are known adverse effects of celiprolol such as headache and tremor that should have been monitored more closely.

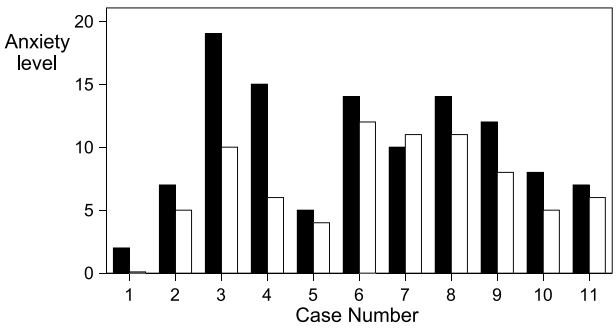

FIGURE 1. Anxiety levels as indicated by HADS-D/A at baseline (black columns) and after 30 days of celiprolol (white columns).

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Beta Blockers for Violence Prophylaxis *Case Reports*

To the Editors:

Psychiatrists use beta blockers to manage aggressive patients.[1] This practice was first reported in 1977.[2] Published evidence is largely limited to case reports and small studies in specific populations, which have focused on patients with mental retardation, posttraumatic organic brain syndromes, and dementia.[3] Few studies have been randomized and controlled. Greendyke[4,5] published 2 double-blind, placebo-controlled studies describing the beneficial effects of beta blockers in patients with organic brain disease. Two other studies used a double-blind, placebo-controlled design to demonstrate that beta blockers reduce aggression in patients with schizophrenia.[6,7] In this paper, we present 2 case reports—1 inpatient and 1 outpatient—describing the successful use of beta blockers for violence prophylaxis in situations unique from existing reports.

INPATIENT CASE REPORT

Mr A, a 40-year-old man with a primary diagnosis of schizoaffective disorder, bipolar type, had a long-standing delusion that he was a wealthy, powerful Mafia boss. He was admitted to the state hospital by court order after threatening several family members and his guardian. He presented similarly for many of his approximately 25 previous hospitalizations. He also had several arrests for violent acts and had been kicked out of multiple group homes for aggressive behavior. He had been treated over the years with numerous combinations of antipsychotics, mood stabilizers, and benzodiazepines. In the emergency room, he was irritable, manic, and threatening. Upon arrival to the inpatient unit, he threatened staff, screamed profanity, and was difficult to redirect.

The treatment team coordinated with his guardian to restart fluphenazine decanoate. When approached about this plan, the patient screamed profanities, threatened to kill staff, ripped off his shirt, and attempted to hit staff with pieces of furniture. He was placed in 4-point restraints. He remained irritable and aggressive over the next 2 weeks while the treatment team made medication adjustments, with little benefit. He continued threatening his family members and guardian, who remained fearful and pushed for long-term placement in a locked facility. Over the following weeks, his behavioral outbursts included punching his mother in the face, violently attacking another patient, throwing objects at staff, numerous angry phone calls, and threats to "tear this whole place up." During a particularly violent episode, he threatened his treating physician during a profanity-laden tirade, stating in part: "I'm going to find out where you live." He then proceeded to rip off his shirt, punch the wall repeatedly, and throw objects at staff. He was again placed in 4-point restraints.

During hospital week 6, the treatment team discussed alternative interventions. By that time, his delusions of being a Mafia boss were less prominent, but he remained very impulsive and aggressive. At that time, his medication regimen included the following: monthly 100 mg injections of fluphenazine decanoate; clonazepam 1 mg BID; clonazepam 2 mg QHS; quetiapine 800 mg QHS; and trihexyphenidyl 2 mg QID. The patient and his guardian provided informed consent to a trial of pindolol. He was started on 5 mg BID and quickly increased to 10 mg BID.

Within days, he stated that it made him feel significantly calmer and less on edge. He had no outbursts over the next week and earned the highest privilege status in the hospital, allowing him to participate in activities off the unit. He tolerated the pindolol without any side effects or complaints. In addition to routine monitoring of his vital signs, the medication nurse was instructed to check the patient's pulse before administering the pindolol and hold the dose for a pulse below 60. His pulse generally remained around 80. During hospital week 7, he had improved enough to pursue placement. He was accepted to a group home and discharged to that facility. Over the next several months, the group home reported that he was a "model resident," remained adherent with all of his medications, and started working part time for the group home, preparing meals and cleaning.

OUTPATIENT CASE REPORT

Mr B, a 20-year-old man, had a primary diagnosis of antisocial personality disorder. He had been diagnosed throughout his life with numerous psychiatric conditions, most frequently bipolar disorder, and had been hospitalized approximately 50 times. Neither the patient nor his medical record reflected any clear history of a manic episode. He instead described anger problems and mood swings "from minute to minute." He met every criterion for antisocial personality disorder, including childhood-onset conduct disorder. He frequently changed schools as a child, primarily because of behavioral problems. He dropped out of school in 11th grade after being transitioned to an alternative school for his behavioral problems. At the time of the intake, he was receiving disability and had no history of paid employment.

Despite denying any history of legal problems or substance misuse, his medical record detailed both. His arrests included calling in a bomb threat to a school, bringing a knife to school, and several assaults. His substance use history involved abuse of both prescription medications and illicit drugs at various times. Over the years, the patient had been treated using a wide range of psychotropic medications including antipsychotics, mood stabilizers, antidepressants, anxiolytics, and stimulants. He denied benefits from any of them, except for benzodiazepines and stimulants. Neither option seemed to be ideal, given the patient's significant history of substance misuse and lack of prominent attentional or anxiety symptoms.

The patient expressed frustration about feeling "angry all the time" and having trouble controlling his emotions. Because of the patient providing a vague history regarding his substance use history, it was not possible to determine any correlation between his substance misuse and his irritability. He regarded therapy as a waste of time, but was open to pharmacological interventions. At the time, he was taking no medications. He provided informed consent to a trial of propranolol, which was started at 20 mg BID. and quickly increased to 40 mg BID. At his next several appointments, despite missing more than half of his prescribed doses, both the patient and his case worker noted improvement in his temper. The patient was noticeably less agitated during appointments, reported feeling calmer, and was easier to interact with, according to his case worker. He did not report any side effects related to the propranolol. During an appointment 6 months after the propranolol was initiated, he stated that with more regular use, it "takes the edge off." He denied any recent outbursts or violent incidents. He also remained out of the hospital for the entire 6 months while taking propranolol. He subsequently missed his next several appointments without explanation and was lost to follow-up.

DISCUSSION

Beta blockers can be used to manage violent patients in a variety of settings. There are some absolute contraindications to consider, including asthma, bradycardia, atrioventricular block, uncompensated heart failure, and sick sinus syndrome. Prescribers must exercise caution with diabetic patients, as beta blockers can mask tachycardia signifying hypoglycemia. Patients also should be warned that using cocaine while taking beta blockers can potentially create unopposed alpha adrenergic stimulation. When patients are screened appropriately, beta blockers can provide a beneficial, low-risk, cost-effective intervention for violence prophylaxis.

There is limited evidence chronicling the use of beta blockers for violence prophylaxis. This article describes the successful use of this approach in 2 common clinical scenarios. More investigation is needed to determine the safety and efficacy of this practice. The authors are initiating studies to systematically evaluate beta blockers for violence prophylaxis in civilly committed and forensic inpatients at a large state hospital. The authors hypothesize that in addition to decreasing the overall frequency of aggressive acts, beta blockers will most effectively reduce acts of aggression categorized as impulsive from the hospital database.[8]

Identifying an effective and safe treatment for patients prone to impulsive aggression would benefit practitioners in correctional settings, forensic hospitals, and virtually any situation with violent patients. The limited existing literature includes case reports and small studies, which have shown this practice to be both beneficial and safe. This paper presents 2 case reports describing the effective use of beta blockers for violence prophylaxis in inpatient and outpatient settings. The authors hope to contribute to the existing literature through these case reports and future studies.

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Memantine for Posttraumatic Stress Disorder in an Older Veteran

To the Editors:

Posttraumatic stress disorder (PTSD) is often a long-term, disabling condition, especially in combat veterans who have been exposed to severe, recurrent trauma. Randomized control trial data show the α_1-adrenergic antagonist, prazosin, to be effective for PTSD-related nightmares and sleep disturbances.[1] Prazosin has also been shown to effectively treat behavioral problems associated with dementia in older adults.[2] However, medication options might be limited when an older adult with PTSD or dementia, or both, is unable to tolerate prazosin. In this case example, we describe an elderly veteran with severe PTSD symptoms and dementia who was unable to tolerate prazosin but who derived benefit for both his problems by the addition of the uncompetitive *N*-methyl-D-aspartate antagonist, memantine.

Because assessment of PTSD symptoms in persons with cognitive impairment can be a challenge, a Posttraumatic Stress Screen for the Cognitively Impaired (PTSS-CI) has been described for use in long-term care settings.[3] It assesses the severity of 8 symptoms of PTSD during the previous week on a 4-point (from 0 to 3) ordinal scale, with higher scores indicating greater severity of symptoms. The PTSS-CI consists of 2 versions, which are administered to the patient and to a knowledgeable informant concurrently. Notably, patient and staff reports of PTSD symptoms have not been found to be influenced by the level of cognitive impairment on the PTSS-CI, and the instrument has been shown to have reliable psychometric properties, as described in the original publication.[3]

We administered the 2 versions of the PTSS-CI to the veteran and the primary nurse taking care of him, respectively, at 3 different time points. These were before the initiation of memantine therapy in November 2009, at 12 weeks after initiating treatment with memantine in February 2010 (which included a 4-week dose-titration protocol and 8 weeks at the optimal dose recommended), and finally after an additional 6 months of memantine treatment in early September 2010. At each time point, the PTSS-CI was administered for 2 consecutive weeks, every Friday around 1 P.M., to maintain consistency between assessments.

CASE REPORT

The subject is an 85-year-old white male veteran admitted for rehabilitation after a fractured hip after falling out of bed during a nightmare related to traumatic experiences during World War II. He had been attempting to jump out his "foxhole" when he fell out of bed and described his reexperiencing symptoms as a "nonstop movie playing in my (his) head." His condition had been diagnosed as PTSD, and he was in mental health treatment of PTSD and recurrent major depressive disorder for many decades and had received lifetime compensation and care from the Department of Veterans Affairs for his PTSD-related disability.

In addition to PTSD and depression, the veteran was diagnosed with mild-to-moderate dementia during an evaluation by a multidisciplinary team at the time of admission in June 2009, with Folstein Mini Mental State (MMSE) score of 18 of 30 in June 2009 and a score of 17 of 30 later in August 2009. He had been on a maintenance dose of citalopram 40 mg/d for more than 2 years, and no changes to the specific serotonin reuptake inhibitor (SSRI) were made during the period of treatment described in the next paragraphs. The veteran also received consistent psychotherapeutic support for his mental health problems for the duration of his stay at the skilled nursing facility.

Because the sleep disturbance was most notable at the time of admission, a trial of prazosin 1 mg at bedtime was initiated. However, the veteran was unable to tolerate an upward titration of prazosin beyond a dose of 3 mg because of postural hypotension and repeated falls. The total duration of the prazosin trial had been 5 weeks, of which 3 weeks were at 3 mg/d, without any noticeable improvement in his nightmares. Given his limited ability to tolerate medication adverse effects in general and some evidence of potential benefit from memantine for both cognitive impairment and symptoms of PTSD (details in the next paragraphs), a trial of memantine, instead of a cholinesterase inhibitor, was considered. His self-rated PTSS-CI scores were 20 and 18, and his PTSS-CI scores per informant report were 10 and 15 (range, 0–24) for the 2 consecutive weeks immediately before initiating treatment with memantine. He tolerated the memantine titration protocol well, and the recommended dose of 10 mg twice a day was reached during 4 weeks.

During the consecutive assessments using the PTSS-CI, there were clinically significant decreases in his self-reported PTSS-CI scores as follows: mean (SD) scores of 19.0 (1.4) before memantine therapy, 8.5 (2.5) 12 weeks after initiation of memantine, and 8.0 (1.4) after an additional 6 months (total around 9 months) of treatment ($F_{2,5} = 14.03$, $P = 0.03$). Post hoc tests revealed a significant difference between the mean scores before initiating memantine and after 9 months of therapy (mean difference, 11.0; 95% confidence interval, 4.92–17.09; $t_2 = 7.78$, $P = 0.02$), whereas the difference between the initial and the week 12 assessments bordered on statistical significance ($t_2 = 3.90$, $P = 0.06$). Mean (SD) observer-rated PTSS-CI scores at the 3 time points were 12.5 (3.5) before initiation, 7.5 (0.7) after 12 weeks, and 9.5 (0.7) at 9 months ($F_{2,5} = 2.82$, $P = 0.21$), with no significant post hoc comparisons.

The greatest improvements on the PTSS-CI were seen for the symptoms of hyperarousal (startled easily, feeling as if in danger), and the pattern of improvement was similar on both versions of the scale. Although the patient continued to reexperience symptoms and nightmares, no additional instances of violent behavior associated with nightmares were observed during the course of treatment with memantine. There was also a clinically noticeable improvement in the veteran's cognitive functioning, and his MMSE scores had increased to 22 and 19 of 30 at the time of the first and second post-memantine assessments, respectively.

DISCUSSION

The improvement in PTSD symptoms from the addition of memantine to ongoing SSRI treatment observed for this older veteran is similar to the benefits from memantine described in a case series of Vietnam-era veterans with similar problems.[4] This younger cohort of veterans, between the ages of 54 and 59, had similar sleep difficulties and nightmares and had persistent symptoms despite pharmacotherapy with different SSRIs. The decision to initiate a trial of memantine in our veteran was facilitated by the presence of a greater degree of cognitive impairment and a greater risk of intolerance to the unpleasant adverse effects of medications than the younger veterans in the previously mentioned case series might have experienced.

The beneficial effect of memantine is believed to be from its actions on the glutamatergic system. A similar explanation

has been offered for the improvement in PTSD symptoms observed from the addition of the antiepileptic drug, lamotrigine, to an SSRI.[5] At this time, it is also unclear whether the added improvement from memantine is from its independent influence on PTSD symptoms or is some form of augmentation of the ongoing SSRI treatment. Memantine augmentation of SSRI therapy has been reported for obsessive-compulsive disorder, another anxiety disorder characterized by recurrent, intrusive, distressing symptoms.[6]

Current reasoning suggests that the therapeutic response for PTSD symptoms from an SSRI (like citalopram), or a medication like memantine, might be associated with its effects on the hypothalamic-pituitary-adrenal axis.[7] A dysregulation in the hypothalamic-pituitary-adrenal axis in response to stress has been most extensively studied in those with PTSD, and correction of an existing imbalance has been observed with treatments that have demonstrated efficacy, including psychotherapy.[8] Along similar lines, older adults treated with an SSRI for generalized anxiety disorder demonstrated a substantially greater reduction in salivary cortisol levels compared with placebo-treated adults.[9] Whether a different adrenergic agent instead of prazosin, like the β-blocker propranolol, might have any added benefits in this case remains to be investigated. Administration of propranolol has been shown to significantly reduce physiologic responses during script-driven traumatic imagery in those with PTSD.[10]

Our observations should be interpreted in light of the inherent limitations, mostly notable being that these observations were from a single case. Next, the memantine trial was open label, and there was no comparison to a period of treatment with a placebo. Further, statistically significant differences were observed on self-report but not according to the observer ratings and were significant between the first and third assessments only. Finally, although we attempted to be as consistent as possible in obtaining collateral assessments, different nursing staff provided the observer assessments at different time points.

Nonetheless, these observations raise interesting possibilities, especially for older patients with PTSD who might have coexisting cognitive impairment or are unable to tolerate unpleasant adverse effects of certain medications. A lifetime diagnosis of PTSD has been associated with a doubling of the risk of developing dementia later in life, and available data suggest that memantine is a safe and well-tolerated medication, especially by those with dementia.[11,12] Randomized control trials using validated measures of PTSD and involving well-defined outcomes are needed to comprehensively evaluate whether memantine holds any promise in these clinical situations. Pending the results of such an investigation, this case underscores the possibility of an alternate therapeutic option that might benefit especially older adults with persistent symptoms of PTSD.

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