Effect of Tandospirone on Mismatch Negativity and Cognitive Performance in Schizophrenia
A Case Report

To the Editors:

Disturbances of cognitive function, evaluated by neurophysiological[1–3] and psychological[4] measures, have been shown to predict outcome in patients with schizophrenia. Mismatch negativity (MMN) is an event-related potential (ERP) generated in response to occasional variations of acoustic stimuli and is suggested to reflect preattentive cognitive operations.[5] Specifically, reduced MMN amplitudes in response to frequent-deviant stimuli have been associated with the pathophysiology of schizophrenia, including decreased gray matter volumes of the prefrontal cortex and superior temporal gyrus.[6]

A limited number of studies report the ability of dopamine,[7] serotonin (5-HT),[7–11] and *N*-methyl-D-aspartate acid (NMDA)[9] transmissions to modulate MMN in healthy human subjects. Here, we report a case of schizophrenia in which adjunctive use of tandospirone, a 5-HT_{1A} partial agonist and anxiolytic,[12,13] was effective for enhancing MMN and improving cognitive performance.

CASE REPORT

The patient is a 37-year-old woman meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for schizophrenia. She graduated from a mainstream high school and entered a university. At age 20, she experienced auditory hallucinations, delusion of persecution, and emotional instability and was admitted to a local psychiatric hospital immediately after the police spotted her wandering around in the rain. After discharge, she gave up studying and took a part time job, which did not last long because of social withdrawal despite treatment with haloperidol (up to 6 mg/d) and sulpiride (up to 150 mg/d). At age 35, she was rehospitalized because of severe auditory hallucinations, delusion of persecution, thought disturbance, and stupor. Switching to monotherapy with olanzapine at 20 mg/d was effective in treating these symptoms, and the patient was discharged after a 3-month hospitalization.

Although her general psychiatric conditions remained relatively well, she occasionally reported anxiety, which became more frequent and severe when she began to take care of her nephew whose mother had obtained a job. At this time, the patient was able to help the household of her brother's family, which she lived with, but was not motivated enough to go out by herself. For anxiolytic purpose, tandospirone, 30 mg/d as initial dose, was added, which was titrated to 60 mg/d (recommended maximum dose) during the initial month, because of the insufficient effect of the lower dose. The dose of olanzapine was unchanged. By 3 months after the start of tandospirone, her anxiety symptoms almost disappeared, and remained so at 6 months. By this time, she gained motivation to shop at a grocery store by herself and pursue her favorite hobbies (embroidery and others).

Electroencephalograms (EEG) were recorded before the start of tandospirone and 3 and 6 months thereafter, according to a regimen previously reported.[14] Mismatch negativity, in response to frequency-deviant tones, was measured with an oddball paradigm. Auditory stimuli were delivered binaurally through headphones with interstimulus intervals of 0.5 second. Deviant tones of 1500 Hz were randomly presented in a series of standard tones of 1000 Hz,

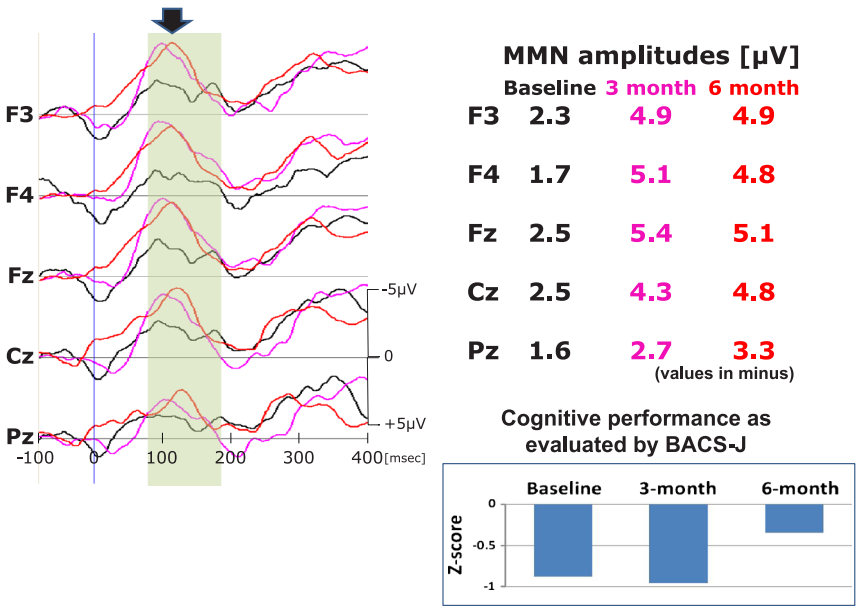

FIGURE 1. Effect of adjunctive use of tandospirone, a 5-HT_{1A} partial agonist, on MMN in a patient with schizophrenia receiving olanzapine. Mismatch negativity amplitudes (indicated by an arrow) in response to frequent-deviant stimuli were increased both at 3 and 6 months after the addition of tandospirone. Inset: cognitive performance, as evaluated by the Brief Assessment of Cognition in Schizophrenia-Japanese version (BACS-J) composite score, was improved at 6 months compared with baseline.

with the presentation probability of 0.1 for the deviant tones. During the recordings, subjects were requested to watch animation. All electrodes were referred to the average amplitude of ear electrodes (bandwidth, 0.16–120 Hz; notch filter, 60 Hz). Electrode impedance was less than 10 kΩ. Data were collected with a sampling rate of 500 Hz. Averaging of ERP waves and related procedures were performed using EPLYZER II software (Kissei Comtec, Co Ltd, Nagano, Japan). The epoch was 600 milliseconds, including a 100- millisecond prestimulus baseline. Neuropsychological assessment was conducted with the Brief Assessment of Cognition in Schizophrenia-Japanese version (BACS-J)[15] at the electroencephalogram measurement. Alternate forms, where appropriate, were used at reassessments. Written informed consent was obtained for these clinical evaluations.

As shown in Figure 1, MMN amplitudes were increased as early as 3 months from the start of augmentation therapy with tandospirone and remained so at 6 months. The BACS-J composite scores (in *Z*-score) at baseline, 3 months, and 6 months were −0.88, −0.95, and −0.32, respectively (Fig. 1, inset), suggesting improved performance after a 6-month adjunctive treatment.

DISCUSSION

To our knowledge, these findings provide the first evidence for the ability of 5-HT_{1A} partial agonists to improve MMN in subjects with schizophrenia. So far, only a limited number of neurochemical manipulations have been reported to enhance MMN in healthy volunteers, for example, 5-HT reuptake inhibitors,[10,11] tryptophan depletion,[8] and nicotinic receptor stimulation,[5] whereas *N*-acetyl-cysteine, a glutathione precursor, has been shown to enhance MMN in patients with schizophrenia.[16] Whether increased or decreased serotonergic tones enhance MMN amplitudes has been controversial,[7,8,10,11] suggesting a role for specific 5-HT receptor subtypes, such as 5-HT_{1A} and 5-HT_{2A} receptors, in the modulation of MMN. It is likely that the deficits in MMN before the start of tandospirone treatment were due to chronicity of the illness (>17 years), rather than a possible influence of olanzapine, for example, actions on 5-HT_{2A} receptors.

The addition of tandospirone was associated with a favorable effect on behavioral performance as evaluated by neuropsychological assessments, consistent with previous reports that 5-HT_{1A} agonists, for example, tandospirone,[12,13] buspirone,[17] and perospirone,[14,18] ameliorated cognitive deficits related to frontal lobe function in subjects with schizophrenia. It is noteworthy that the change in MMN waveforms preceded the improvement of behavioral performance during treatment (Fig. 1). This divergence in time suggests that some of the electrophysiological signals reflecting preattentive cognitive process may be able to predict treatment efficacy in neuropsychological performance.

The effect of 5-HT_{1A} agonism on MMN may be mediated by its influence on glutamatergic and, possibly, GABAergic function. This assumption is based on observations that blockade of NMDA receptors reduces MMN[9,19] and that 8-OH-DPAT, a 5-HT_{1A} agonist, modulates cortical activity through 5-HT_{1A} receptors located on GABAergic interneurons and those on pyramidal neurons.[20] Further study is needed to confirm the potential benefit of agents acting on 5-HT_{1A} receptors for improving MMN and other components of ERPs in people with schizophrenia.

AUTHOR DISCLOSURE INFORMATION

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Hyperprolactinemia and Atypical Antipsychotic Therapy in a Case of Fatal Thromboembolism

To the Editors:

CASE REPORT

A 19-year-old woman presented with a first episode of flat affect, psychomotor retardation, auditory hallucinations, and delusions. She was of Antillean origin, and she had no known medical problems and no personal or family history of psychiatric disorders or substance abuse. A diagnosis of psychosis not otherwise specified was retained. She elected to be treated with a combination of second-generation antipsychotics (SGAs), risperidone 5 mg and olanzapine 10 mg, to limit detected adverse effects such as hyperprolactinemia and weight gain and was rapidly discharged.

She was readmitted 5 days later with relapse of her symptoms. She refused to eat and became actively suicidal, committing repetitive and very serious attempts. Symptoms of major depression became evident. Pharmacological treatment brought no clear benefits and permission of electroconvulsive therapy was granted by the court. She required pharmacological treatment for maintenance of remission. The combination of olanzapine 10 mg, risperidone 2 mg, venlafaxine 225 mg, and nortriptyline 100 mg was used in her case probably to limit the unwanted adverse effects of each individual drug and because the symptoms had also been very severe, posing significant danger to her life. She nonetheless gained a significant amount of weight, approximately 70 lb, and had hyperprolactinemia with secondary amenorrhea. An electrocardiogram revealed a normal QTc at 402 milliseconds. She was discharged 3 months after her initial admission.

During outpatient follow-up, olanzapine was reduced to 5 mg daily, and risperidone was discontinued. The patient remained functional and euthymic until 13 months after her last discharge. At the time of recurrence, a psychosocial stressor and the fact that she had abandoned her medication due to frustration with her weight gain were identified. She became isolated, anhedonic, and refused to eat or drink. Risperidone was reintroduced at 1 mg twice a day, and she was readmitted to the inpatient ward. The mental examination revealed a young woman with moderate excess weight, significant psychomotor retardation, flat affect, perplexity, negation of her symptoms, minimal collaboration, and refusal of most vital signs and all laboratory tests. She had a severe thought disorder and offered only a few words that made it possible to identify suicidal thoughts and probable psychotic symptoms.

Olanzapine was ceased as the patient had been obsessed with her weight gain, and risperidone was increased to 1 mg morning and 2 mg before bedtime. The next morning, the patient was sitting down and writing, to be found 7 minutes later lying on the floor, unconscious, superficially breathing with low blood pressure. The medical team arrived almost instantly, and she had no pulse, was not breathing, and had fixated mydriasis. Reanimation measures proved unsuccessful, and an hour later, the patient was pronounced dead. The last medications received were loxapine 25 mg + diphenhydramine 25 mg and risperidone 2 mg + nortriptyline 100 mg the evening before.

On the basis of the pathologist's report, the coroner concluded to massive bilateral pulmonary emboli elucidating a link to the use of nortriptyline and risperidone. The autopsy identified tremendous overdosage of nortriptyline and venlafaxine, but this was attributed to postmortem redistribution. Risperidone was at an infratherapeutic dosage.

It should be noted that there was no identified cause of venous stasis such as immobility or use of physical restraints. She had not used oral contraceptives. There was no mention of homocysteinemia or raised level of antiphospholipid antibodies in the patient's file. A previous cerebral scanner had revealed no anomaly.

DISCUSSION

There are a number of studies reporting an association between pulmonary venous thromboemboli, sometimes fatal,[1] and SGAs, in particular clozapine and olanzapine. Such vascular phenomena have been described since the 1960s for first-generation antipsychotics (FGAs). It was later identified that SGAs pose a greater risk than FGAs do and that lower-potency FGAs pose a greater risk than higher-potency FGAs do. Odds ratios vary from 2.39 for low-potency FGAs to 6.9 for SGAs.[2] Although no evident explanation exists for this association, many underlymechanisms have been proposed: interference with 5-hydroxytryptamine 2 receptors on platelets, raised levels of antiphospholipid antibodies, venous stasis exacerbated by sedation or physical restraints, and hyperhomocysteinemia.[3] Hyperprolactinemia is also identified as a potential risk factor,[4] with prolactin having recently been recognized as a potent platelet aggregation coactivator.[5] No increased risk of thromboembolism has been shown in past users of antipsychotics. Polypharmacy was hypothesized as a possible confounder, and some studies have found current use of an antidepressant as conferring greater risk (odds ratio = 4.9).[6] To our knowledge, no increased risk of thrombolembolus is associated with venlafaxine or nortriptyline specifically.

In a study on the in vitro effects of antipsychotics on human platelet aggregation and plasma coagulation involving clozapine, olanzapine, risperidone, and haloperidol,[7] clozapine was the only drug that increased platelet aggregation and adhesion.

There seem to be few studies or reports of thromboemboli on risperidone therapy. Borras et al[8] reported a 25-year-old patient with no known risk factors for thromboembolism who developed pulmonary embolus thrice: once under olanzapine therapy and twice under risperidone therapy. Kamijo et al[9] studied Japanese patients who experienced idiopathic pulmonary thromboembolism and found that 44% of their sample (7 patients) had antipsychotic use, and in 2 cases, the antipsychotic was risperidone. Interestingly, more women than men were affected, and patients developed symptoms in the early morning. Risperidone was identified in 1 study as

doubling the risk of venous thromboembolism among elder nursing-home residents.[10]

In conclusion, it is reasonable to suspect that risperidone, as other SGAs, must be considered as plausibly increasing the risk of thromboemboli, and careful evaluation of risks versus benefits is further needed in cases where known risk factors for thromboemboli are already identified, such as in our case, namely the patient's significant weight gain, polypharmacy, concomitant use of antidepressants and low-potency FGAs, and, most notably, hyperprolactinemia. Further studies are needed on the prothrombotic risk associated with SGAs and the possible mechanisms involved.

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Effectiveness of Risperidone for the Treatment of Nightmares in Veterans With Posttraumatic Stress Disorder

To the Editors:

Recurrent nightmares and sleep continuity disruptions are the 2 major sleep disturbances included for posttraumatic stress disorder (PTSD) criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*). Reports of sleep abnormalities among combat veterans with PTSD have ranged from 59% to 73%.[1] Posttraumatic stress disorder–related nightmares may exert a serious impact on patients' social, occupational, and personal functioning (*DSM-IV-TR*).

In a review of the pharmacological treatment of nightmares and insomnia in PTSD, Van Liempt et al[2] noted that there are insufficient controlled studies to derive evidence-based guidelines. The literature on the treatment of nightmares with atypical antipsychotics in PTSD is scarce and inconclusive. Reports of one case treated with quetiapine,[3] 5 cases with olanzapine,[4] and 4 of 5 cases with aripiprazole[5] document some success for atypicals in the treatment of PTSD sleep disturbances. No reports were found using clozapine and ziprasidone. Risperidone has a modest literature support for treating PTSD symptoms including sleep disturbances with nightmares.[6–10] However, none of the risperidone literature has investigated risperidone as a therapy specifically for the treatment of PTSD-related combat nightmares.

The 2 principal research questions addressed in this retrospective study are the following: Is risperidone effective as a dedicated medication for combat nightmares? Is risperidone's effectiveness related to the concurrent use of other psychiatric medications or to concurrent substance abuse? The study is intended to identify indications for future prospective studies.

In this retrospective study, approved by the institutional review board, cases from both the inpatient and outpatient services were reviewed. The diagnosis of PTSD was based on the *DSM-IV-TR* criteria. Demographic characteristics included age, sex, race, and marital status. Multiple patient profile characteristics, and prior or concurrent substance abuse and psychotropic medications were included in the study.

Inclusion criteria for the study were nightmares associated with combat-related PTSD, initiation of risperidone treatment specifically noted to be for nightmare suppression, and a follow-up visit with clinical notes that referenced the exact treatment response. The follow-up notes had to permit classification of risperidone response as 1 of 3 possible outcomes: full response with no recall of nightmares, partial response with reduction in frequency and perceived intensity, and no response, with unchanged nightmare frequency or intensity. Sixty-five cases met all the inclusion criteria. Additional comorbid diagnoses included other anxiety disorders (15), substance disorders (61), mood disorders (47), cognitive disorders (10), personality disorders (8), and adjustment disorders (4). The length of treatment ranged from 1 month to 9.8 years for veterans seen primarily in one clinic.

Risperidone dosing ranged from 0.5 to 4.0 mg a day. Prior and concurrent psychiatric medication groups (antidepressants, anxiolytics, benzodiazepines, opioids, anticonvulsants, hypnotics, and antipsychotics) were recorded as present or absent. All atypical antipsychotics were discontinued before starting risperidone treatment, whereas the other psychiatric medications were often begun before risperidone and continued throughout the months of the veteran's treatment with risperidone.

In the statistical analysis, continuous variables were expressed as mean ± SD. Categorical variables were expressed as numbers and percentages of totals. A priori established clinically relevant independent variables were compared across response categories by using χ^2 tests for linear trend. $P < 0.05$ was considered statistically significant. Statistical correlations for patient groups with less than

TABLE 1. Comparisons of Full, Partial, and No Risperidone Responses in Veterans With and Without Prior and/or Concurrent Use of Psychotropic Medications

	No. Patients Who Used Medications				No. Patients Who Did Not Use Medications					
Psychotropic Medications	**Full**	**Partial**	**No**	**Total**	**Full**	**Partial**	**No**	**Total**	**No. Patients With Missing Data**	***P***
Antidepressants	18	16	8	42	10	10	2	22	1	0.514
Anticonvulsants	8	8	5	21	19	17	5	41	3	0.313
Anxiolytics	5	6	3	14	23	20	7	50	1	0.422
Hypnotics	11	7	3	21	17	19	7	42	2	0.445
Benzodiazepines	9	14	5	28	18	12	5	35	2	0.215
Opioid agonists	9	9	1	19	19	17	9	45	1	0.319
Prior atypical antipsychotic use	1	7	4	12	27	19	6	52	1	0.004*

*Significant *P* value.

10 cases were not considered meaningful indices for conclusions. Statistical analyses were performed using Stata statistical package version 10 (Stata Corp, College Station, Tex).

Among the 65 veterans treated with risperidone for PTSD-related nightmares, 55 (84.6%) reported changes in nightmare patterns. Full nightmare cessation was noted in 28 patients (43.1%), and partial response was found in 27 patients (41.5%). All full responders reported cessation of nightmare recall on the first night. Partial responders reported a decrease in the frequency and intensity of nightmares on the first and following nights. Risperidone response was consistent for the full and partial responders from the first week of treatment. Two of the veterans who reported complete cessation of nightmares with risperidone at 2.0 mg/d had no other concurrent psychiatric medications. Lack of response to risperidone was noted in 10 veterans (15.4%).

The demographic profile revealed a predominately male (95.3%), white (72.3%), and married (69.2%) population with a mean age of 57.4 years (range, 27–82 years). All *P* values for the demographic characteristics and response to risperidone were greater than 0.05, indicating no significant correlation.

Effective risperidone doses ranged from 0.5 to 4.0 mg/d, with 92.7% of the fully and partially responding veterans receiving risperidone doses from 0.5 to 2.0 mg/d. There was no statistically significant correlation between the risperidone dose and the treatment effect within this dosage range ($P = 0.868$). There were no data indicating attempts to lower or increase doses.

Of the 8 veterans receiving low risperidone dose (0.5 mg/d), 50.0% responded fully and 25.0% responded partially. Of the 20 veterans on 1.0 mg of risperidone, 33.3% responded fully and 57.1% responded partially. Fifty percent of the 32 veterans receiving 2.0 mg had complete cessation of nightmares, whereas 31.3% had a partial result. Of the patients on 3.0 mg (n = 3) or 4.0 mg (n = 1), 25.0% experienced no nightmares, whereas 75.0% had partial responses.

Adverse effects in 11 cases included hand tremor, headaches, nausea and vomiting, drowsiness, irritability, gastric irritation, generalized weakness, enuresis, urine retention, and weight gain. In these cases, risperidone doses ranged from 0.5 to 2.0 mg administered over a period of 1 month to 5 years. Eight veterans with adverse effects had responded fully and 3 responded partially. Adverse effects were reported to have ceased after discontinuation of risperidone.

There was no statistically significant correlation between risperidone treatment in veterans with prior or concurrent alcohol abuse/dependence (n = 36) compared with veterans without such a history. Similarly, no statistically significant correlations were found between risperidone treatment response and abuse/dependence of other substances (cocaine, cannabis, opioids, tobacco, benzodiazepines, and caffeine). In addition, both full and partial positive treatment responses to risperidone were reported regardless of the prior or concurrent use of multiple combinations of psychotropic medications (antidepressants, anticonvulsants, anxiolytics, hypnotics, benzodiazepines, and opioid agonists; Table 1). The one exception was the statistically significant correlation for risperidone treatment in veterans with prior atypical antipsychotic use ($P = 0.004$). Compared with those patients who were antipsychotic naive, the 12 veterans with prior exposure to antipsychotics had proportionally fewer full responses (8.3% vs 51.9%) and greater no responses (33.3% vs 11.4%).

The precise mechanism by which the risperidone might affect PTSD symptoms is not clear. Risperidone has high antiserotonergic receptor antagonism and antidopaminergic activity (5-HT_{2A}, 5-HT_7, D_2), which theoretically play an important role in reducing anxiety and insomnia.[11] In addition, risperidone's α-1 adrenoreceptor blockade may modulate trauma nightmares by decreasing light sleep and normalizing rapid eye movement sleep.[12,13]

The results of this study suggest that low-dose risperidone is effective in stopping the memory of nightmares or reducing the frequency and intensity in combat veterans with PTSD. This effect seems to be independent of the prior and/or concurrent use of other psychiatric medications and of the prior and/or concurrent use of illicit substances. Only prior exposure to atypical antipsychotics seems to reduce response to risperidone. Future prospective studies are needed to further investigate these results.

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Development of Asymptomatic Pancreatitis With Paradoxically High Serum Clozapine Levels in a Patient With Schizophrenia and the CYP1A2*1F/1F Genotype

To the Editors:

Pancreatitis secondary to clozapine has been occasionally reported (see Supplemental Table A [Supplemental Digital Content 1, which shows reports of clozapine-associated pancreatitis, http://links.lww.com/JCP/A30] and Supplemental online material, Background [Supplemental Digital Content 2, http://links.lww.com/JCP/A31]) and attributed to toxic blood levels of clozapine. Interference with liver metabolic breakdown is believed to be the main culprit. The CYP 1A2 isoenzyme is reported to account for the largest part of the disposition of clozapine, yielding desmethylclozapine,[1] although other isoenzymes, such as 3A4, which is mainly responsible for N-oxide formation[2] and, to a lesser extent, 2D6, seem to play some minor role in eliminating clozapine from the blood. Clozapine seems to be a weak inhibitor of the 2D6 isoenzyme.[3] The roles of clozapine and its metabolites on exocrine pancreatic function have not been thoroughly investigated.

We report a case of pancreatitis shortly after institution of clozapine treatment. The patient showed elevated serum clozapine levels and hyperglycemia, but not hyperlipidemia, and improved after discontinuation. She redeveloped pancreatitis at rechallenge with a lower dose of clozapine.

CASE REPORT

A 40-year-old white woman with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, schizophrenia, paranoid type, had been involuntarily admitted to our acute care unit for psychotic exacerbation. At admission, she was persecutory and delusional. She had auditory hallucinations, psychomotor agitation, and dysphoric mood. She was overweight (body mass index, 30) and dressed in a bizarre way. All her routine laboratory tests were in the normal range, including blood glucose, cholesterol, low-density lipoprotein cholesterol, and triglycerides. She proved to be negative to alcohol and drug screening tests. A heavy smoker (40–60 cigarettes per day), she reported no recreational substance use (alcohol and coffee). She scored 95 on the BPRS (see Supplemental online material, Rating scales, Psychopathology [Supplemental Digital Content 2, http://links.lww.com/JCP/A31]).

The patient's objective psychiatric history dates back to age 20 years, when she presented with frank psychotic symptoms, comprising persecutory delusions with bizarre characteristics focusing on sexual issues, auditory hallucinations of multiple conversing voices, psychomotor agitation, and aggressive behavior. Her first hospitalization, at age 21 years, had been involuntary. Since that time, she has

been followed by the National Health Service's Community Outpatient Facilities; she received high-dose haloperidol (up to 15 mg/d) and switched to high-dose risperidone (10 mg/d) during the last 3 years. She also was receiving 7.5 mg/d lorazepam. Her response to treatment was rated as partial. Since her twenties, she has been hospitalized several times, compulsorily on most occasions. She never reached a satisfactory level of remission or insight. Before her last exacerbation, she had completely discontinued antipsychotic medication.

Because of unsatisfactory response to previous treatments, after washout (see Supplemental online material, Washout [Supplemental Digital Content 2, http://links.lww.com/JCP/A31]), we introduced 25 mg/d oral clozapine, gradually reaching 300 mg/d in 1 month, with a serum clozapine level of 831 ng/mL (therapeutic range, 350–600 ng/mL),[4] whereas norclozapine was 243 ng/mL, as measured through liquid chromatography/tandem mass spectrometry techniques (Q-Trap 2000; Applied Biosystems, Foster City, Calif; our method was similar to that by Aravagiri and Marder[5]). We administered clozapine in 2 divided doses, at 9 A.M. and 9 P.M., and withdrew blood for serum clozapine testing at 12 hours. We also administered 10 mg lorazepam to exploit its antianxiety and hypnotic properties. We were alerted for possible adverse events, but 1 week later, the patient showed to be more insightful and her psychosis had improved (BPRS score, 41); hence, we changed her hospitalization regimen from involuntary to voluntary and, regretfully, did not modify the dose regimen. After 1 month at ward, her blood glucose level rose to 459 mg/dL for the first time; this was approximately 10 days after clozapine assay. In the same time, her blood cholesterol had risen to 256 mg/dL (reference range, 120–220 mg/dL) and blood triglycerides to 342 mg/dL (reference range, 50–180 mg/dL). We found elevated pancreatic enzymes during routine laboratory testing, with the patient complaining of no physical symptoms; pancreatic amylase was 116 U/L (reference range, 8–53 U/L) and pancreatic lipase peaked at 759 U/L (reference range, 20–300 U/L) 2 days later, whereas total serum calcium was slightly lower than normal for the first time and persisted for further 3 days (8.1 mg/dL; reference values, 8.4–10.2 mg/dL); erythrosedimentation rate was 69 mm/h (reference range, 0–20 mm/h), and C-reactive protein was 8.25 mg/dL (reference range, 0–0.5 mg/dL). Emergency abdominal ultrasounds showed no abnormality; however, computerized tomography and magnetic resonance cholangiography, despite confirming no abnormalities in the biliary tract, revealed the existence of a radio-opaque gallstone in the infundibulum. We immediately started tapering off clozapine, concluding the process in 6 days; concomitantly, we started the patient on oral haloperidol, 4 mg/d. We added appropriate antibiotic (see Supplemental online material, Antibiotic treatment [Supplemental Digital Content 2, http://links.lww.com/JCP/A31]) and subcutaneous insulin lispro and insulin glargine in variable doses, depending on her blood glucose levels. Her cholesterol dropped to 142 mg/dL and her triglycerides to 302 mg/dL. Ten days later, she had recovered completely from her pancreatitis, and all laboratory measures were normal. She scored 42 on the BPRS. She was discharged with 4 mg oral haloperidol, thence transferred to a long-stay community rehabilitation center. There, she was rechallenged with clozapine at the dose of 100 mg/d. One week later, she was again hyperglycemic and with elevated pancreatic enzymes, although less than in the preceding episode; hence, she returned to our unit. We immediately suspended clozapine and instituted again the same antibiotic and insulin regimen as above. We withdrew blood for measuring serum clozapine level 4 hours after last clozapine intake; she had 364 ng/mL clozapine and 165 ng/mL norclozapine, which is within the therapeutic window. We introduced 4 mg/d oral risperidone and 800 mg/d oral carbamazepine and reintroduced the high-dose benzodiazepine as above. On this occasion, we withdrew a 5-mL blood sample for DNA extraction, to analyze cytochrome P450 isoenzymes 1A2 (CYP1A2) and 3A4 (CYP3A4) (see Supplemental online material, Pharmacogenomics [Supplemental Digital Content 2, http://links.lww.com/JCP/A31]).

She quickly improved (BPRS, 40) and returned to the community rehabilitation center, where physicians abstained from treating her with clozapine once more.

She provided full, free, informed consent for DNA analysis, treatments, and procedures during her hospital stay after commutation of the involuntary to voluntary hospitalization regimen, as well as for the publication of her case.

DISCUSSION

We report a case of pancreatitis in a patient with treatment-resistant schizophrenia who took clozapine. It is supported that existing pancreatitis increases clozapine blood levels.[6] However, we consider this mechanism to be unlikely in our case, at least as concerns the induction phase. In fact, baseline values of pancreatic values were normal.

We classified the event as definitely associated with clozapine (see Supplemental online material, Rating scales, Attribution of side effect and classification [Supplemental Digital Content 2, http://links.lww.com/JCP/A31]).

Pharmacogenomic analysis showed the patient to be a normal clozapine metabolizer (see supplemental online material, Pharmacogenomics, for further discussion [Supplemental Digital Content 2, http://links.lww.com/JCP/A31]). Overall, there were no identifiable genetic reasons for which clozapine plasma levels should be so high with both full and reduced doses of clozapine in the absence of other concomitant factors (but sensitization may be considered as a possibility).

Clozapine, like olanzapine, under certain conditions, may form a toxic transient nitrenium$^+$ intermediate metabolite (see Supplemental online material, Nitrenium toxicity [Supplemental Digital Content 2, http://links.lww.com/JCP/A31]). This mechanism may be reasonably advocated for pancreatitis caused by planar atypicals, such as clozapine and olanzapine, rather than for agranulocytosis, which is more caused by fluperlapine than olanzapine, yet the former lacks a nitrenium intermediate.

Furthermore, we may hypothesize that there has been a sensitization to the pancreatic exocrine effect of clozapine because it reoccurred at a much lower dose approximately 2 weeks after she had recovered. Learning might have contributed to sensitization.

Therapeutic drug monitoring is not suggested as routine procedure for clozapine.[7] Among all reports on clozapine-associated pancreatitis (see Supplemental Table A [Supplemental Digital Content 1, http://links.lww.com/JCP/A30] and Supplemental online material, Comparison to other clinical reports [Supplemental Digital Content 2, http://links.lww.com/JCP/A31]), the only reported blood clozapine values were those by Schmitz-Hübsch et al,[8] which were in the therapeutic range, as were levels at rechallenge in our case. In our case, we recorded higher levels than the therapeutic window would allow at first assay; we presume that these had to do with the first occurrence of pancreatitis and that the second episode occurred at therapeutic serum levels because of sensitization.

Our case compares with other cases reported in literature and differs from many of them in several aspects (see Supplemental Table A [Supplemental Digital Content 1, http://links.lww.com/JCP/A30] and Supplemental online material, Comparison to other clinical reports [Supplemental Digital Content 2,

http://links.lww.com/JCP/A31]). One of the criteria to establish the strength of the association with a given side effect is the disappearance of the effect upon discontinuation and its reappearance after rechallenge. Comprising our report, 7 cases were rechallenged with clozapine; in 5 cases, pancreatitis did reoccur, and in 2, it did not (see Supplemental Table A [Supplemental Digital Content 1, http://links.lww.com/JCP/A30] and Supplemental online material, Comparison to other clinical reports [Supplemental Digital Content 2, http://links.lww.com/JCP/A31]).

IMPLICATIONS FOR CLINICAL CARE

The fact that pharmacogenomic results did not match actual clozapine serum levels shows that it is premature to conduct expensive genomic analyses for clinical purposes and that therapeutic drug monitoring should be given priority in hospital settings. The prediction that the extreme interindividual variations in clozapine and its metabolites' blood levels[9] could be explained by different genes working on the cytochromes that are responsible for clozapine metabolism was not fulfilled. Suspected pancreatitis should be an added indication to the recommendations by Greenwood-Smith et al[7] for investigating clozapine serum levels. When administering clozapine, biliary and pancreatic function deserve special attention because current or past gallstones may have sensitivity to the impact of clozapine on pancreatic function; pancreatic enzyme testing should become routine when treating patients with clozapine or other new-generation antipsychotics that have the potential to derange glucose and lipid metabolism. The finding of off-window blood clozapine levels should prompt physicians to modify dosage.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest for the present study; however, in the past 2 years, Dr Tatarelli has participated in Advisory Boards for Schering, Servier, and Pfizer and received honoraria from Schering, Servier, and Pfizer.

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Diazepam Discontinuation Through Agomelatine in Schizophrenia With Insomnia and Depression

To the Editors:

Schizophrenia is a chronic psychiatric disorder characterized by distortion of thinking and perception and by an inappropriate or blunted affect. Although sleep disorders do not pertain to the clinical core of its symptoms, it affects the quality of life of schizophrenic patients.[1] Several sleep disorders have been described in patients with schizophrenia, insomnia,[2] arrhythmic circadian rest-activity cycles,[3] and sleep-disordered breathing.[4] Pharmacological strategies to treat insomnia in schizophrenia include adding sedative antipsychotics and the use of hypnotics.[5]

Agomelatine, a new antidepressant with norepinephrine-dopamine disinhibition properties because of its antagonism

on the 5-hydroxytryptamine 2C receptor,[6] has recently been approved by the European Medicines Agency and has proved to be effective in the treatment of moderate to severe major depressive disorder.[7] Agomelatine is also a potent agonist at melatonin receptors.[6] Melatonin is the main pineal hormone that plays a major role in the induction and regulation of sleep.[8] Schizophrenic patients with insomnia have been reported to benefit from melatonin treatment.[9] Melatonin has also been used to diminish benzodiazepine intake in patients with insomnia.[10]

In this article, we describe the case of a patient with chronic simple schizophrenia and severe insomnia and depression that only had a partial response to high doses of benzodiazepines and sedating antipsychotics. Treatment with agomelatine permitted the patient to completely suspend benzodiazepines.

CASE REPORT

Mr Y is a single 36-year-old man diagnosed with simple schizophrenia (*International Classification of Diseases, 10th Revision*, F20.6). He started psychiatric treatment at the age of 16 years. Since the beginning of the disease, the patient has complained of problems with insomnia, initiating and maintaining sleep that had never remitted. He has been treated with several typical and atypical antipsychotics for his schizophrenia as well as with sedative antipsychotics and hypnotics for his sleep problems. In the last 5 years, apart from his psychotic disorder, the patient's sleep problems moved to the forefront of the clinical picture and were the core of the patient's complaints. In the last 3 years, the treatment that the patient followed was stable and consisted of 100 mg of diazepam, 300 mg of levomepromazine, and 120 mg of clotiapine every night. All medication was orally administered. In the last year, the patient presented a moderate depression that was treated with 60 mg of duloxetine (by mouth) in the morning. His mood improved with the prescribed treatment, but 11 months later, it worsened.

To treat the worsening of mood, we proposed that the patient suspend duloxetine and introduce agomelatine, in an attempt to treat at the same time the mood worsening and the sleep disorder. To measure the intensity of depression, the Montgomery-Åsberg Depression Rating Scale[11] (MADRS) was applied. In the basal measurement, before introducing agomelatine, the MADRS score was 24, indicating a moderate depression. Agomelatine was introduced at the dose of 12.5 mg at dinner during 4 days, whereas duloxetine was reduced to 30 mg in the morning for the same period. On the fifth day, agomelatine was increased to 25 mg at dinner whereas duloxetine was suspended. The antipsychotic treatment was kept stable while the patient was instructed to reduce 10 mg of diazepam every week until the next appointment 1 month later.

In the next appointment, the patient had completely suspended the intake of diazepam 1 week before the appointment. The patient had an improved sleep quality, but he was still complaining of depressed mood. The MADRS score was 20, and the main improvement of the score was in item 4 (reduced sleep) that had gone from 4 points in the first evaluation to 0 points in the second evaluation.

The next appointment was set for 1 month later, and we asked the patient to reduce 25 mg of levomepromazine every week until the next appointment. Because mood had not improved, agomelatine was increased until 37.5 mg at dinner. During this appointment, once again, the patient had completely suspended levomepromazine in 3 weeks when he was asked to reduce only 100 mg in 4 weeks. The patient looked healthier and related that his mood had improved. The MADRS score at this point was 9. The patient did not present any sleep complaint with the treatment.

Treatment indications for the next appointment included reducing clotiapine from 120 to 80 mg, with a tapering strategy of reducing 20 mg of clotiapine every 2 weeks. The next appointment was programmed 1.5 months later. Two weeks after the last appointment, the patient had a relapse that was characterized mainly by aggressiveness and initiating and maintaining sleep. Restoration to the initial dose of levomepromazine (300 mg before bedtime) controlled the clinical picture. In the next appointment, the patient was clinically stable and without sleep problems. The treatment was as follows: 37.5 mg of agomelatine at dinner and 300 mg of levomepromazine and 120 mg of clotiapine before bedtime.

Three months later, the patient was clinically stable, without sleep problems and following the same treatment. The patient has been on agomelatine treatment for a total period of 7 months.

DISCUSSION

According to what we know so far, this is the first case in which agomelatine has successfully been used as a treatment of insomnia and depression in a schizophrenic patient being treated with high doses of benzodiazepines and sedating antipsychotics. Although the European Medicines Agency–approved agomelatine indication is for the treatment of major depression, initial studies with agomelatine were focused on its hypnotic properties.[12]

Insomnia in schizophrenia affects the psychopathology and quality of life of patients. Severe insomnia is one of the prodromal symptoms of psychotic relapse and is a relapse-predicting factor.[13] Although insomnia problems should be taken into account in the global treatment of psychosis, we believe that agomelatine may be an alternative to consider when schizophrenic patients present depression and insomnia. It may be argued that agomelatine's disinhibitory effect on the dopaminergic system may act as a triggering factor of psychotic episodes. This risk has to be considered, and patients should be controlled frequently to check whether psychotic symptoms appear.

As far as we know, there are no reported cases of psychotic episodes attributable to agomelatine treatment. However, this risk with another antidepressant (bupropion), with a norepinephrine-dopamine reuptake inhibitor mechanism of action, has been reported.[14] We still have to wait for the generalization of agomelatine use to know whether this risk exists with agomelatine. Although our patient had a relapse while on agomelatine, from our point of view, it was precipitated because the patient had suddenly stopped the treatment with levomepromazine. In fact, after levomepromazine restoration, the clinical picture remitted. The fact that controlled discontinuation of benzodiazepines in patients with chronic schizophrenia has not produced psychotic relapses[15] supports our interpretation about the cause of the relapse.

To our knowledge, there are no data on the use of agomelatine in schizophrenia. Therefore, our results with 1 patient should be considered as preliminary until more data or studies with bigger sample size are published.

AUTHOR DISCLOSURE INFORMATION

None of the authors have conflict of interest to declare.

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A Comparison of Antipsychotic Drug-Defined Daily Doses Versus Chlorpromazine Equivalent Doses in Patients With or Without Extrapyramidal Motor Symptoms

To the Editors:

Whereas antipsychotic drugs share the common property of reducing the symptoms of psychosis, they represent a structurally diverse range of compounds with distinct neurochemical and pharmacokinetic properties. Despite these differences, a number of guidelines have been developed to allow direct comparison of dosing between different antipsychotic drugs. These include the expression of antipsychotic drugs as a defined daily dose (DDD) or as a chlorpromazine equivalent (CE) dose.[1,2] The DDD is the international unit of drug use approved by the World Health Organization for drug use studies. Values are determined by researchers of the World Health Organization collaborating centre of drug statistics methodology. The DDD is defined as the "assumed average maintenance dose per day for a drug used in its main indication in adults." Using DDD provides a convenient method to compare dosing between different drugs. Furthermore, it allows calculation of the cumulative dose of antipsychotic drugs irrespective of whether they are used as a single agent or as part of an antipsychotic polypharmacy regimen. Chlorpromazine equivalent doses are well established in the scientific literature and have been used to compare dosing both within and between different classes of antipsychotics. Values for chlorpromazine equivalency are based on a number of different factors, including dopamine D_2 receptor occupancy and dosing used in registration and other clinical trials, although the index has been criticized for its lack of transparency in determining individual drug values.[3] Unlike DDDs, CE doses are not based solely on dosing for the primary indication.

The most common use of standardized drug dosing for antipsychotics has been to compare the therapeutic properties of the drugs. However, an important property of any antipsychotic dosing framework should include its ability to predict the drug's adverse effects,[4] as tolerability is a major issue in antipsychotic treatment adherence and can potently affect quality of life. To our knowledge, there has never been a direct comparison between the DDD and CE dosing systems of the motor adverse effects of antipsychotic drugs, which include the extrapyramidal symptoms (EPS). The purpose of the present study was thus to examine antipsychotic dosing in a large diagnostically heterogeneous population, using the 2 different guidelines, and determine how well each predicted the presence of EPS.

Patients were recruited from 8 different community mental health teams in Vancouver, British Columbia.[5] These teams provide individuals living in defined catchment areas with psychiatric resources, including assessment, treatment, medication management, and rehabilitation. The study protocol was approved by the University of British Columbia Research Ethics Board and conducted in accordance with the principles of Good Clinical Practices and the Declaration of Helsinki. A total of 788 patients who gave written consent to have their medical profiles reviewed were screened for the study. The inclusion criteria required that: (1) the patient's diagnosis was schizoaffective disorder, schizophrenia, bipolar disorder, depression, or psychosis not otherwise specified; (2) the patient's comprehensive medication profile was available through BC PharmaNet (a provincewide electronic network linking all British Columbian pharmacies to a central set of data systems; prospective studies have confirmed that PharmaNet accurately predicts treatment adherence for oral medications in chronic illness[6]); (3) the patient be treated with at least one antipsychotic; (4) the patient did not receive any depot antipsychotic; and (5) the patient had been treated with the same medications and doses for at least 90 days; thus, antipsychotic dose was calculated after anticholinergics were introduced.

Data collected from BC PharmaNet included antipsychotics and anticholinergics. The presence of EPS in patients was inferred from scripts for anticholinergic medications. Demographic data were

obtained from patients' medical charts. Dosing for the oral antipsychotics was compared by converting to multiples of the DDD or CE doses. Multiples of the DDD were obtained by dividing the prescribed daily dose (PDD) by the DDD. The DDD values were extracted from the Anatomical Therapeutic Chemical Classification System.[7] Chlorpromazine equivalent doses were calculated according to the *Clinical Handbook of Psychotropic Drugs*[8]; CE values provided by this source have been used in numerous studies in the literature by ourselves and other research groups.[9] Values were added for subjects prescribed more than one antipsychotic concurrently. For statistical analysis, the average antipsychotic dose for patients with and without EPS, as calculated by CE doses and PDD/DDD ratios, was compared using the Wilcoxon signed rank test (significance, $P < 0.05$). Comparison of frequencies was performed using the χ^2 test.

A total of 406 subjects met the inclusion criteria. The average age of subjects was 47.1 years, and sex was split evenly (Table 1). The most common diagnosis of subjects was schizophrenia followed by schizoaffective disorder, bipolar disorder, major depression, and psychosis not otherwise specified. A total of 61 patients were prescribed anticholinergic medications for the treatment of EPS; the most commonly used drug was benztropine (75% of the subjects; mean dose, 1.7 mg) followed by procyclidine (21% of the subjects; mean dose, 8.7 mg) and trihexyphenidyl (4% of the subjects; mean dose, 6.0 mg). Analysis of demographic variables did not indicate any significant differences between those subjects treated with anticholinergics and those who were not. A higher proportion of the subjects treated with anticholinergics than those who were not had a diagnosis of schizophrenia ($P < 0.005$). When the mean total antipsychotic dose per day was calculated according to the PDD/DDD ratio, there was no significant difference between those treated with or without anticholinergic drugs (Table 1). However, the difference in antipsychotic dosing between the groups was highly significant when CE doses were analyzed instead ($P < 0.005$). This effect was not restricted exclusively to either the atypical or the typical drugs. Analysis of mean drug doses for the subjects who were medicated with only atypical antipsychotics (n = 342) indicated that although there was no difference in PDD/DDD ratios between those treated with anticholinergic drugs and those who were not treated, there was a significant difference when doses were calculated as CE doses ($P < 0.005$). When subjects treated with only typical antipsychotics were considered (n = 32), the difference in mean daily dose between those treated with anticholinergic drugs was not different for PDD/DDD ratios, but there was a strong trend for CE doses ($P = 0.09$).

TABLE 1. Summary Characteristics and Chlorpromazine Equivalent Doses (CE) Versus PDD/DDD Ratios for Subjects With (+) and Without (−) EPS

	+EPS (n = 61)	−EPS (n = 345)	*P*
Age ± SEM, y	48.1 (1.3)	46.9 (0.7)	0.450
Sex, male (%)	54.2	49.3	0.481
Diagnosis			
Schizoaffective disorder (%)	23.0	17.7	0.33
Schizophrenia (%)	52.5	33.3	<0.005
Bipolar disorder (%)	9.8	20.0	0.06
Depression (%)	4.9	13.3	0.06
Psychosis NOS (%)	3.3	7.8	0.20
Antipsychotic dose (± SEM)			
All antipsychotics (n = 406)			
PDD/DDD	1.29 (0.24)	1.16 (0.05)	0.67
CE	263.3 (41.4)	160.3 (7.0)	<0.005
Atypical agents only (n = 342)			
PDD/DDD	1.32 (0.14)	1.18 (0.05)	0.22
CE	203.6 (17.6)	151.4 (6.7)	<0.005
Typical agents only (n = 32)			
PDD/DDD	1.00 (0.53)	0.34 (0.08)	0.25
CE	459.6 (211.8)	140.3 (35.7)	0.09

DISCUSSION

The present study compared daily antipsychotic dosing using both the DDD and CE guidelines in a diagnostically heterogeneous outpatient psychiatric population. The main finding is that when dosing is compared between these 2 methods of calculation in the subjects with or without EPS, only the CE approach reliably detects a difference between these 2 groups. When all subjects were considered, mean CE daily doses were 1.64 times higher in the subjects with EPS than in those without EPS, but only 1.11 times higher for PDD/DDD ratios. Interestingly, this difference remains significant in the subjects treated with only atypical antipsychotic drugs and exhibited a strong trend toward significance in the subjects treated with only typical agents despite the latter group's small sample size. Thus, calculation of antipsychotic drug dosing with the CE method has better heuristic value in predicting whether motoric adverse effects will occur in relation to the dose of the drug used. When comparing between drugs, a system is required that reflects the elevated risk for EPS as drug dose increases. Based on the present study, converting all antipsychotic drugs into a standardized value as the CE dose largely retained this important property.

To our knowledge, this is the first study to evaluate 2 different dosing guidelines on the ability to detect differences in drug-induced adverse effects rather than therapeutic efficacy. The reason for this difference in dosing protocols is not immediately apparent. The CE dose is based in part on D_2 receptor affinity, and thus, increasing CE will be predictive of increased D_2 receptor occupancy, with a greater risk for EPS. This may explain why a greater proportion of subjects with schizophrenia than any other diagnosis exhibited EPS, as dosing was highest in this group. However, this effect should be most pronounced for typical drugs, as higher doses of these are more likely to exceed the level of D_2 receptor occupancy needed to induce EPS, yet we observed large and significant differences for CE doses in the subjects with EPS who were being treated with only atypical antipsychotic drugs. It is, therefore, likely that some antipsychotic drugs are "weighted" more heavily in each dosing approach than the other, and the drugs that increase the risk for EPS are weighted more heavily in the CE than the DDD dose protocol. Greater transparency in the determination of drug dose values remain a controversial and complex issue, and alternate strategies for values have been proposed, such as using expert clinical consensus.[4]

Further study of this issue is strongly warranted, as standardized drug dosing guidelines are helpful in analyzing patterns of antipsychotic drug use in large heterogeneous clinical populations with diverse patterns of antipsychotic drug use.[1,2] Others have already advocated for

developing new instruments of antipsychotic drug dose standardization that take greater account of the risk for drug adverse effects.[4] As a caveat to the present study, the use of anticholinergic scripts as a proxy for EPS (despite its widespread practice) has several limitations: the signs of EPS can be subtle and therefore overlooked or misdiagnosed, the prescription of anticholinergics may be based on the subjective decisions of physicians, and patients may continue to be treated with anticholinergics even after being switched to a different antipsychotic and no longer experiencing EPS. Prospective studies addressing this issue with quantitative neurological scales are needed. Despite this limitation, the present data provide strong evidence to indicate that CE dosing may be more useful than PDD/DDD ratios when calculating standard drug doses in relation to the motoric adverse effects of these drugs.

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Alterations in Pain Perception During Benzodiazepine Withdrawal
A Case Series

To the Editors:

Increased pain perception is a typical symptom of benzodiazepine withdrawal, which is combined with increased glutamatergic neurotransmission.[1] Increased glutamatergic neurotransmission has been assumed to modulate nerve growth factor (NGF) expression.[2] Both increased glutamatergic neurotransmission and increased NGF expression are thought to contribute to hyperalgesia.[3] In contrast, benzodiazepines are thought to decrease pain perception by modulation of GABAergic neurotransmission.[4] Here we present 4 cases of benzodiazepine-dependent patients in which we observed alterations in NGF plasma levels, mechanical pain threshold (MPT), and mechanical pain sensitivity (MPS).

In total, we investigated 4 inpatients (3 men [26, 54, and 61 years] and 1 woman [37 years]) with depressive disorder and comorbid benzodiazepine dependence according to *International Statistical Classification of Diseases, 10th Revision* and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (Department of Psychiatry and Psychotherapy, University of Erlangen-Nuremberg, Germany) before (day 1) and after completion of benzodiazepine withdrawal (day 2; diazepam equivalent dose, 0 mg). Benzodiazepine withdrawal was done by continuous tapering of the dose benzodiazepine patients took usually (lorazepam in 2 patients, diazepam in 1 patient, oxazepam in 1 patient). Diazepam equivalent doses were 15 (3 patients) and 30 mg (1 patient) on admission. Patients had no further Axis 1 diagnosis and no severe somatic illnesses. Patients were not treated by electroconvulsive treatment and transcranial magnetic stimulation. All patients received stable doses of antidepressant medication (tricyclic antidepressants). Intensity of benzodiazepine withdrawal was measured using the Clinical Institute Withdrawal Assessment—Benzodiazepines (CIWA-B).[5,6]

Nerve growth factor plasma levels were assessed using the DuoSet enzyme-linked immunosorbent assay Development System (DY293 B; R&D Systems,

TABLE 1. QST and NGF Measurements Obtained in the 4 Patients Investigated

	Patient 1, 65, Male	Patient 2, 26, Male	Patient 3, 54, Male	Patient 4, 37, Female	*P*
MPT (day 1)	103.97 (116.00)	10.56 (82.00)	168.90 (116.00)	29.86 (77.00)	0.62, 0.44
MPT (day 2)	32.00	73.52	9.19	27.86	0.01, 0.44
MPS (day 1)	0.56 (0.47)	1.66 (0.66)	0.44 (0.47)	2.93 (0.73)	0.21, 0.55
MPS (day 2)	2.87	0.36	0.82	3.49	0.14, 0.55
NGF (day 1), pg/mL	148.90 (151.37 [60, male])	168.50 (28.80 [26, male])	159.90 (94.59 [54, male])	163.60 (135.50 [30, female])	0.08, 0.60
NGF (day 2), pg/mL	239.60	184.40	172.10	112.10	0.09, 0.60
CIWA-B score (day 1)	45.00	42.00	41.00	29.00	0.11
CIWA-B score (day 2)	28.00	41.00	34.00	24.00	0.11

Control levels are displayed in parentheses. *P* values refer to group-to-group analysis between patients and healthy controls (first value) and alterations during withdrawal in the patient's group (second value).

Wiesbaden-Nordenstadt, Germany). All the assays were performed according to the manufacturer's direction. Nerve growth factor serum levels of the patient group were compared with NGF serum levels of healthy controls. Controls were negative for any psychiatric disease and received no psychopharmacological treatment.

MPT and MPS were investigated using a standardized program.[7,8] Mechanical pain threshold was assessed using weighted pinprick mechanical stimulators (flat contact area of 0.2 diameter) that exerted forces of 8, 16, 32, 64, 128, 256, and 512 nM. The stimulators were applied in a 2-second on-off paradigm until patients reported a feeling of sharpness. Final threshold was determined by the geometric mean of 5 series of ascending and descending stimuli. Mechanical pain sensitivity was assessed using the same 7 weighted pinprick stimulators. Pain intensity was recorded on a numerical rating scale reaching from 0 (no pain) to 100 points (most intensive pain intensity). Results obtained from QST were compared with normative data according to Rolke et al.[7]

The investigation was conducted in accordance with the Declaration of Helsinki of 1975 (revised 2008) and approved by the local Ethics Committee of the University of Erlangen-Nuremberg. Each participant gave written informed consent.

Group-to-group analyses between the healthy control group and the patient group were assessed by the *t* test for independent samples. Alterations of measurements during benzodiazepine withdrawal were assessed using *t* test for dependent samples. Data were analyzed by GraphPad Prism 5.0 (GraphPad Software Inc, San Diego, Calif). We found a tendency toward decreased MPT in the benzodiazepine-dependent patients, which decreased further during withdrawal (Table 1). Concordant with this result, MPS was tendentially increased in benzodiazepine-dependent patients before and after benzodiazepine withdrawal (Table 1). Nerve growth factor plasma levels were tendentially increased in benzodiazepine-dependent patients in the same time frame (Table 1 for details).

DISCUSSION

Benzodiazepines have been consistently reported to modulate pain perception.[9] Preclinical studies suggest an association between decreased pain perception and anti-inflammatory properties of benzodiazepines.[10,11] Other results show an association between decreased pain intensity and modulation of GABAergic neurotransmission afforded by benzodiazepine treatment.[12,13]

Expression of NGF is known to be increased in neuroinflammation.[14] Other study results suggest an association between increased glutamatergic neurotransmission and increased NGF expression.[2] Increase in NGF expression and NGF signaling via the TrkA receptor has been associated with increased pain perception and in particular with hyperalgesia.[15,16]

Here, we presented 4 cases of benzodiazepine-dependent patients in which we observed decreased MPT and increased MPS. Nerve growth factor plasma levels were significantly increased in the same time frame. Mechanical pain sensitivity increased during benzodiazepine withdrawal. Benzodiazepine-dependent patients showed high CIWA-B scores (>15 points) mirroring subjective perception of intensive withdrawal symptoms. Therefore, these preliminary results may be interpreted as effects resulting from increased glutamatergic neurotransmission during benzodiazepine withdrawal leading to the typical benzodiazepine withdrawal symptom of hyperalgesia.

The results obtained from the 4 cases reported here point toward the possibility of an association between benzodiazepine withdrawal, pain perception (MPT and MST), and NGF expression. Nevertheless, these preliminary results have to be justified in controlled studies investigating larger samples. Moreover, explanatory power of the results obtained here is limited not only by the small number of patients investigated, but also by their depressive comorbidity, antidepressant treatment, lack of standardization of benzodiazepine treatment, and lack of blindness to dose tapering. In conclusion, quantitative sensory testing objectivised withdrawal-induced hyperalgesia in benzodiazepine patients during withdrawal. Moreover, NGF was increased in the benzodiazepine patients, who had high intensity of benzodiazepine withdrawal. Therefore, increased glutamatergic neurotransmission due to benzodiazepine withdrawal may account to the alterations observed here. Controlled studies are necessary to justify these preliminary results.

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A Case of Catatonia Successfully Treated With Ziprasidone, in a Patient With *DSM-IV* Delusional Disorder

To the Editors:

CASE REPORT

Our patient is a 52-year-old man who was urgently admitted to the psychiatric clinic with delusional beliefs of religious content, social isolation, and refusal to eat or drink.

The patient had a 16-year history of delusional disorder of unspecified type, and he was treated with haloperidol. He had discontinued haloperidol 3 months earlier. At the onset of the illness, the patient presented briefly with delusional jealousy, which was soon replaced with hyperreligiosity; he gradually developed delusional ideas of religious content. He joined a conservative denomination and became increasingly involved, assumed an extreme ascetic lifestyle, ultimately deciding to become a monk. His preoccupation with religious matters became increasingly intense, and he was eventually admitted under an involuntary commitment order. He was diagnosed with delusional disorder of unspecified type and discharged with oral haloperidol. While on haloperidol, he maintained a baseline level of hyperreligiosity but returned to his previous level of functioning and resumed work. He remained employed throughout the 15 years that ensued and has never experienced hallucinations or other perceptual disturbances, thus consistently fulfilling the *Diagnostic and Statistical Manual of Mental Disorder* criteria for delusional disorder. On one occasion, he discontinued haloperidol, and delusional ideas of religious content reemerged. Upon resuming medication, the symptoms disappeared.

Three months before admission, he discontinued medication again and delusional ideas of religious content reappeared. Four days before admission, he started a continuous total fast. He refrained from eating or drinking anything. At the same time, he exhibited an exacerbation of his baseline hyperreligiosity, spent hours reading various religious books, and stopped working. During an all-night vigil at a monastery, he was found lying down in a rigid state; he resisted any passive movement of his limbs. He was transported to our department thereafter.

Upon admission, he exhibited religious delusional ideas, complained of persistent blasphemous thoughts (curses against saint figures), and refused food and drink. Admission global assessment of function score was 20, Brief Psychiatric Rating Scale (BPRS) score was 43, and Bush-Francis Catatonia Rating Scale (BFCRS) score was 8. Intravenous fluids were administered. He remained mostly motionless in bed and seemed to be praying for most of the time. On the third day, the patient exhibited worsening negativism, mutism, and ultimately waxy flexibility. At that time, the patient had a Brief Psychiatric

Rating Scale score of 50 and a BFCRS rating of 25; results of electroencephalogram, brain computed tomographic scan, and a full laboratory workup were negative.

With his autonomic status being stable, a formal diagnosis of nonmalignant catatonia was made. Given the need to manage an acutely delusional patient and the lack of electroconvulsive therapy availability, we chose to administer an atypical agent available parenterally and started the patient on ziprasidone at an initial dosage of 40 mg 4 times a day.

On the fourth day, waxy flexibility, negativism, and rigidity resolved; the patient resumed voluntary motor activity, and this is reflected as a BFRCS scale score of 9. Given the positive response, we increased ziprasidone to 40 mg 2 times a day. On the fifth day, mutism and negativism resolved. The patient was able to give account of his history, and BFCRS score dropped to 5. The patient remained hospitalized for a total of 38 days. Upon discharge, his GAF score was 85. At follow-up, he had returned to work, resumed daily activities, and attended church on Sundays, without delusional or otherwise excessive preoccupation. At 6 weeks after discharge, his family confirmed that he has returned to the premorbid level of functioning.

DISCUSSION

Catatonia is an established psychomotor syndrome characterized by signs and symptoms of motor behavior and volition. Catatonia is associated with a variety of psychiatric and systemic medical illnesses and toxic states.[1] The treatment of catatonia traditionally included benzodiazepines and electroconvulsive therapy.[2] Administration of antipsychotic agents was generally contraindicated, as first-generation antipsychotics worsened rather than relieved catatonia.[3,4] Other drugs that regulate glutamatergic transmission, such as amantadine[5] and memantine,[6] have also been used. Second-generation antipsychotics, particularly for schizophrenic patients predisposed to catatonia, were only subsequently evaluated as a possible treatment alternative.[7]

In the current diagnostic criteria (*Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition*), catatonia is not recognized as a separate disorder but is technically restricted to a feature of schizophrenia despite its frequent association with numerous psychiatric and medical conditions. Sporadic yet increasing evidences indicate that the claim for an independently classifiable catatonic syndrome has nosologic validity.[3] A relatively recent study found a high prevalence of catatonia[8] (between 7% and 17%) among immediate psychiatric admissions. It is reasonable to claim that availability of a syndrome-independent catatonic specifier will facilitate identification of catatonic symptoms in diseases outside the psychotic spectrum. Our case further supports this claim, as we present a case of catatonia in a patient with a long-established history of delusional disorder, an unusual clinical picture.

There is a lack of inferential studies regarding superiority of benzodiazepine treatment over antipsychotics.[9] Despite traditional usage of benzodiazepines in cases of acute catatonia, chronic catatonia generally does not respond to benzodiazepines.[10] It seems that diagnosis of schizophrenic illness is a negative predictive factor for benzodiazepine efficacy.[11] Although the literature lacks conclusive data regarding the use of atypical agents in catatonia, it has been suggested that catatonic symptoms may markedly respond to antipsychotic agents.[12,13] The mechanism of this effect remains largely unknown, but a complex interaction between GABA, glutamate, dopamine, and serotonin is postulated,[14] the latter 2 relating to the atypical agents' usage in this clinical setting. Successful treatment of catatonia in our patient with the atypical agent ziprasidone is in line with evidence that atypical agents may be an option in the treatment of nonmalignant catatonia.

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The authors have nothing to declare.

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Partial Compliance as Determined From Plasma Levels of Sertraline and Its Metabolite in Depressed Patients in Primary Care

To the Editors:

Compliance to antidepressant treatment has been recognized as an important factor regarding optimal treatment outcome.[1–4] Patients are active, and treatment regimens are modified rather than being completely accepted or rejected.[5] Thus,

partial compliance is an increasing problem, and it has been demonstrated that less than 50% of primary care patients with depression have complete compliance.[6–8]

Therapeutic drug monitoring (TDM) is an established method for assessing compliance in the treatment of depression.[9–11] Traditionally, only the parent substance has been taken into account. However, our research group has previously improved the validity of TDM by including also the major metabolite and scrutinizing the metabolite/parent substance ratio and its changes over time,[12] that is, the TDM-RSM (TDM–ratio screening method).

To validate and to further develop the method by identifying partially noncompliant patients and to determine the consequences on response to treatment, TDM-RSM was applied post hoc on a large study population of patients with a diagnosis of major depression and treated in primary care. The details of the study are reported by Åkerblad et al,[13] but the main objective was to measure the effect of an educational compliance enhancement program and the effect of TDM (presence or absence of sertraline in serum) on drug compliance and treatment response. Included in the present study are the 782 patients (mean age, 50 years; range, 19–95 years; 73% women) from the original study[13] who had completed 24 weeks' treatment with sertraline dosed according to the clinical routine. Scheduled visits were at weeks 4, 12, and 24, and at each visit, the patients were asked if the drug had been taken as prescribed. To be regarded as compliant, a "yes" had to be recorded at all 3 visits. Treatment response was assessed by means of the Montgomery-Åsberg Depression Rating Scale[14] and the 2 Clinical Global Impression scales, Severity and Improvement.[15] Extensive training sessions were held for all participating general practitioners. To be classified as a responder at week 24, the patient had to have a reduction from baseline in total Montgomery-Åsberg Depression Rating Scale of at least 50%, a Clinical Global Impression–Severity score indicating normal to mildly ill, and a Clinical Global Impression–Improvement score indicating much or very much improved. Finally, serum drug concentration samples were obtained as trough values under steady-state conditions. The serum samples were all analyzed at the same laboratory using an established validated high-performance liquid chromatography with ultraviolet detection.[16] The limit of quantification was 1.53 ng/mL (5 nmol/L).

According to the published TDM-RSM,[12] patients with quantifiable serum concentrations of sertraline and desmethylsertraline in all samples are considered to be compliant. Noncompliant patients have no detectable concentrations of either parent substance or metabolite in 1 or more of the samples. Partially noncompliant patients are those having, in at least 1 sample, a desmethylsertraline/sertraline ratio outside 2 SDs of a population mean ratio and a ratio deviating at least 50% from the patient's own mean value.

All serum samples on the 782 patients were scrutinized. Two thousand seventy-six samples had quantifiable levels of sertraline and desmethylsertraline (median sertraline concentration, 11 ng/mL [25th–75th percentile, 7.3–17.5 ng/mL]; desmethylsertraline, 29.4 ng/mL [19.2–44.8 ng/mL]; desmethylsertraline/sertraline ratio, 2.8 [2.2–3.3]; coefficient of variation [CV, logarithmic values] for interindividual ratio, 21%; CV intraindividual ratio, 23%). The mean desmethylsertraline/sertraline ratio ±2 SDs interval (back transformed from log scale to original scale) was between 1.30 and 5.85.

Six hundred twenty patients were defined as compliant according to the definition. Ninety-six patients had a desmethylsertraline/sertraline ratio outside ±2 SDs. Of these, 81 patients had at least 1 ratio deviating more than 50% from his/her own mean ratio or no quantifiable metabolite and were consequently defined as partially noncompliant. Equally many, 81 patients, were defined as noncompliant. To exclude that a drug-drug interaction could be the cause of a deviating ratio, all concomitant medications taken by patients with deviating ratios or with unquantifiable samples were compared with all pharmacokinetic C and D interactions listed in the Swedish physician desk reference book (FASS) and in Swedish Finnish Interaction X-referencing (SFINX).

Partial noncompliance and total noncompliance were about equally common in men and in women; 27.2% of the noncompliant patients and 35.8% of the partially noncompliant patients were men (χ^2_1 = 1.40, not statistically significant). Furthermore, whereas 63% of the noncompliant patients admitted that they had not taken the medication as prescribed, only 25.9% of the partially noncompliant patients admitted it (and 12.6% of the compliant patients revealed inconsistency in drug intake when questioned, according to TDM-RSM). Finally, there were significantly more responders among the compliant patients as compared with partially noncompliant or noncompliant patients (Table 1).

DISCUSSION

The main finding was that, by applying TDM-RSM, it is possible to identify partially noncompliant as well as totally noncompliant patients. Thus, the method previously described by us[12] was validated.

It is of considerable interest that whereas a majority of the noncompliant patients admitted being noncompliant when questioned, it was acknowledged only by a minority of the partially noncompliant patients. The validity of the concept of partial noncompliance is further strengthened by the different response rates found between patients with full compliance and patients with partial noncompliance.

The number of compliant and partially noncompliant patients is of the same magnitude, indicating, in line with earlier results,[5] that partial noncompliance is an important problem. By using conventional dichotomized TDM technique (presence or absence of parent compound in serum), partially noncompliant patients will not be found.

Identifying partially noncompliant patients is of great importance to understand insufficient treatment response. Therapeutic drug monitoring–ratio screening method, as described, can be applied in everyday clinical practice. However, the method has not yet been tested on other drugs than sertraline. Thus, the results should not be generalized to other drugs before further studies are made.

TABLE 1. Relationship Between Compliance According to TDM-RSM and Response to Treatment After 24 Weeks of Treatment With Sertraline

Compliance According to TDM-RSM		Response at Week 24 (LOCF)
	n	n
Noncompliance	81	46 (56.8%)
Partial noncompliance	81	56 (69.1%)
Compliance	620	511 (82.4%)
	χ^2_2 = 32.34, P < 0.001	

LOCF indicates last observation carried forward.

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Impact of Antidepressant Treatment History on Clinical Outcomes in Placebo and Medication Treatment of Major Depression

To the Editors:

Previous courses of antidepressant treatment have been related to subsequent decrements in medication response. The Sequenced Treatment Alternatives to Relieve Depression Trial, for example, used a design where subjects who did not remit during initial citalopram treatment received successive treatment alternatives until achieving remission or reaching the end of 4 treatment levels. An overarching finding was that of progressively lower rates of response and remission observed at each level.[1] Retrospective studies also have found lower rates of antidepressant response associated with an increased number of previous drug exposures,[2–4] a phenomenon referred to as *stepwise tachyphylaxis*.[4]

Biological and/or psychological mechanisms may explain the association between previous antidepressant history and subsequent decrements in response. Previous antidepressant treatment overlaps with "treatment-resistant depression," defined as 1 or more failed antidepressant trials in the current episode.[5,6] In this view, previous treatment might serve as a proxy for an inherently less tractable form or course of depression or a form or course of depression that is less responsive to intervention with conventional pharmacological agents. Tolerance mechanisms also may operate such that repeated exposure to antidepressant medication itself begets physiological adaptation and corresponding diminution of clinical response. In this vein, stepwise tachyphylaxis has been observed independent of treatment-resistant depression.[2] Psychological mechanisms as well, including patient expectations, negative cognitions, and classical conditioning phenomena, may play a role in decreased response after previous antidepressant failure.[7] Previous treatment has been shown as a factor in placebo response[8] as well as medication response, but the potential differential impact across treatments is not known.

We addressed the relationship between treatment history and subsequent medication and placebo treatment outcomes examining data from 72 Major Depressive Disorder (MDD) outpatient subjects who completed 1 of 3 double-blind placebo-controlled antidepressant treatment trials[9] at the UCLA Laboratory of Brain, Behavior, and Pharmacology. The trials used identical recruitment procedures, inclusion/exclusion criteria, and design features except for the active medication (fluoxetine or venlafaxine). Subjects did not differ significantly across trials on age, sex, or symptom severity. Screening consisted of a standard clinical evaluation, a structured clinical interview (Structured Clinical Interview for Axis I *DSM-IV* Disorders–Patient Edition, version 2.0),[10] and the 17-item Hamilton Depression Rating Scale ($HamD_{17}$).[11] Persons having psychotic symptoms or cluster A or B Axis II disorders were excluded. Enrollees had $HamD_{17}$ scores of 16 or higher at entry and were free of psychotropic medications for 2 weeks prior.

All subjects received a 1-week placebo lead-in before 8 weeks of randomized double-blind treatment with medication (fluoxetine 20 mg or venlafaxine 150 mg; n = 37) or placebo (n = 35).[9] Venlafaxine was dosed at 150 mg after 10 days; fluoxetine dosing

TABLE 1. Clinical and Demographic Characteristics of the Sample by Treatment Assignment and Treatment History

	Total Sample (n = 72)	Medication Group (n = 37)	Placebo Group (n = 35)	Test	Treatment-Naive (n = 31)	Treatment-Experienced (n = 41)	Test
Age, y (±SD)	41.68 (12.08)	42.73 (12.30)	40.57 (11.91)	$t_{70} = -0.76$; $P = 0.45$	40.48 (12.33)	42.59 (11.96)	$t_{70} = -0.73$; $P = 0.47$
Sex (% female)	60%	62%	57%	$\chi^2 = 0.19$; $P = 0.66$	45%	71%	$\chi^2 = 4.80$; $P = 0.03$*
Treatment history (% previously treated)	57%	57%	57%	$\chi^2 = 0.001$; $P = 0.97$	NA	NA	NA
Depression severity Initial $HamD_{17}$ (±SD)	20.43 (6.53)	20.00 (6.90)	20.89 (6.18)	$t_{70} = 0.57$; $P = 0.57$	20.65 (6.31)	20.27 (6.76)	$t_{70} = 0.24$; $P = 0.81$
Family history of MDD (% yes)	80%	78%	83%	$\chi^2 = 0.29$; $P = 0.59$	70%	88%	$\chi^2 = 3.47$; $P = 0.06$
No. previous episodes	2.39 (1.68)	2.68 (1.65)	2.09 (1.69)	$t_{70} = -1.50$; $P = 0.14$	2.0 (1.03)	2.68 (2.00)	$t_{70} = -1.73$; $P = 0.09$

*$P < 0.05$.

NA indicates not applicable.

was 20 mg/d. Placebo was administered on the same schedule as active drug within each trial to preserve blinding. In this reanalysis, subjects were classified as either "antidepressant-experienced" or "antidepressant-naive" based on historical information recorded at intake indicating whether they had ever before been treated with an antidepressant medication. Clinical outcomes included change in total $HamD_{17}$ score from baseline to week 8 and remission (final $HamD_{17}$, ≤7).

Antidepressant-experienced subjects (n = 31) did not differ from antidepressant-naive subjects (n = 41) with respect to age or baseline symptom severity (Table 1). However, antidepressant-experienced subjects were statistically more likely to be female and showed trends toward a greater number of previous episodes and a greater likelihood of family history of MDD. Analysis of covariance (ANCOVA) was used to examine treatment history (antidepressant-experienced or antidepressant-naive) along with sex, baseline symptom severity ($HamD_{17}$), and treatment history × treatment type (medication or placebo) interaction as potential covariates to model change in $HamD_{17}$ score over 8 weeks (dependent variable) in the total sample. The overall model was significant ($F_{3,68} = 3.66$, $P = 0.009$) with a significant effect of treatment history ($F_{1,68} = 12.43$, $P = 0.001$). Subjects with no previous history of medication treatment showed greater symptom improvement on the $HamD_{17}$ (mean change, −12.16; SD, 5.62) than did those subjects who had previously received antidepressant treatment (mean, −8.12; SD, 7.61). There was no evidence of an effect of sex ($F_{1,68} = 0.35$, $P = 0.56$) or symptom severity ($F_{1,68} = 0.02$, $P = 0.90$). However, there was a significant treatment history × treatment type interaction ($F_{1,68} = 7.63$, $P = 0.007$).

Subsequent ANCOVAs examining medication and placebo subjects separately found that, among placebo subjects, treatment history was a significant predictor ($F_{3,33} = 9.68$, $P = 0.004$) with $R^2 = 0.23$ and remained significant when controlling for baseline illness severity, sex, number of previous episodes, and family history of MDD ($F_{5,29} = 9.18$, $P = 0.005$). However, ANCOVAs used to examine these same models of symptom change in medication subjects were not significant. We then used χ^2 analysis to examine remission rates to drug versus placebo for antidepressant-naive and antidepressant-experienced subgroups. Whereas there was no statistically significant separation between medication and placebo remission rates in the total sample ($\chi^2 = 1.58$, $P = 0.21$) or in the antidepressant-naive subgroup ($\chi^2 = 0.26$, $P = 0.61$), significant drug-placebo separation was observed in the analysis including only treatment-experienced subjects ($\chi^2 = 5.24$, $P = 0.02$). Among antidepressant-naive subjects, there was no significant difference in change in $HamD_{17}$ scores between subjects who were randomized to medication (mean, −12.19; SD, 5.74) versus placebo (mean, −12.33; SD, 5.69) ($t_{29} = 0.03$, $P = 0.98$). In contrast, among antidepressant-experienced subjects, $HamD_{17}$ change was significantly greater in medication subjects (mean, −10.90; SD, 7.18) as compared with placebo subjects (mean, −5.20; SD, 7.08) ($t_{39} = 2.56$, $P = 0.01$).

DISCUSSION

Overall, subjects with a previous history of antidepressant treatment showed less improvement over 8 weeks of randomized treatment than did antidepressant-naive subjects; however, the effect of previous treatment depended significantly on treatment condition. In this sample, treatment history had a negative impact on placebo response but not on medication response. One consequence of this differential impact of treatment history on medication versus placebo outcomes was that, whereas analysis of the total sample did not find significant drug-placebo separation, analyses that were limited to treatment-experienced subjects found a statistically higher rate of remission in the medication group.

Our observation of greater placebo response among antidepressant-naive subjects is consistent with previous findings.[8] One possible explanation for the observed greater placebo response among antidepressant-naive subjects is that they were simply less ill. Indeed, placebo response has previously been associated with shorter duration of the depressive episode[8] and less severe illness.[9–12] Accordingly, previous reports have consistently found an association between greater depression severity and greater drug-placebo separation.[13–17] In this study, however, treatment history was not associated with symptom severity at intake. Although antidepressant-experienced subjects showed a trend toward a greater number of previous episodes, and a greater likelihood of family history of MDD, treatment history was shown to predict placebo response even when controlling for these clinical characteristics. Another possibility is that the antidepressant-experienced subjects were better able to correctly guess their treatment condition based on previous experience with medication, including side effects, and that this de facto "unblinding"

rendered them less likely to respond on placebo. Treatment-naive subjects on placebo may have been more likely to believe that they were receiving medication. Subjects' greater expectations that they will receive active medication have been linked to higher placebo response rates,[12,14] whereas lower expectations of receiving active medication have been linked to lower placebo response rates and, hence, greater drug-placebo separation.[16]

We did not find a significant effect of treatment history in the medication group. Differences between previous reports[2–4] and the present finding may be due to treatment history measures or the medications studied. We examined antidepressant treatment history as a dichotomous variable accounting for lifetime treatment history, whereas other reports examined treatment history in the current episode, stratified by number of previous trials.[4] Regarding medication, 24 of 37 of our medication subjects had been treated with a mixed reuptake inhibitor medication, venlafaxine, whereas previous reports have suggested greater tachyphylaxis with selective serotonin reuptake inhibitor medications.[18,19]

Results of this study suggest that previous treatment may be an important factor in determining placebo response and drug-placebo separation in placebo-controlled antidepressant treatment trials in MDD. Future work should replicate results in a larger sample and should examine expanded aspects of previous treatment by systematically obtaining information regarding the number and adequacy of trials and nature of response.[20]

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Andrew Leuchter, MD, has provided scientific consultation or served on advisory boards for Aspect Medical Systems, Bristol-Myers Squibb, Eli Lilly and Company, Merck & Co., Otsuka Pharmaceuticals, and Pfizer. He has served on a speaker's bureau for Bristol-Myers Squibb, Eli Lilly and Company, Otsuka Pharmaceuticals, and Wyeth-Ayerst Pharmaceuticals. He has received research/grant support from the National Institute of Mental Health, the National Center for Complementary and Alternative Medicine, Aspect Medical Systems, Eli Lilly and Company, Wyeth-Ayerst Pharmaceuticals, Merck & Co., Pfizer, Sepracor, Vivometrics, and MedAvante. He also is a former equity shareholder in Aspect Medical Systems.

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Antidepressant Treatment Restores Brain-Derived Neurotrophic Factor Serum Levels and Ameliorates Motor Function in Parkinson Disease Patients

To the Editors:

One working hypothesis for motor disturbances observed in Parkinson disease (PD) is that the degeneration of the dopaminergic (DA) neurons of the substantia nigra pars compacta and the resulting loss of their nerve terminals in the striatum are due to decreased levels of trophic factors,[1] survival factors for selected populations of central nervous system neurons.

A body of evidence describes the protective role of brain-derived neurotrophic factor (BDNF)[2] on midbrain DA neurons, whereas glial cell–derived neurotrophic factor (GDNF), which belongs to a family of related proteins that include neurturin, artemin, and persephin, supports the development and survival of mesencephalic DA neurons.[3] These findings have generated considerable excitement about the possibility to establish a therapy with neurotrophic factors for PD.

Interestingly, antidepressant drugs may bust brain production of trophic factors, an effect associated with improvement of clinical symptoms. Depression is a common psychiatric disorder in PD occurring in approximately half of patients.[4] Preclinical studies have found that chronic antidepressant treatment increases the expression of BDNF and neurogenesis in the adult rat hippocampus,[5,6] and intracerebral infusion of BDNF itself produces antidepressant effects.[7] Also, the mood stabilizers, lithium and valproate, increase GDNF levels, both in vivo and in vitro.[8,9] Consistent with these animal studies, increased BDNF expression was recently found in hippocampal regions in subjects treated with antidepressant medications at the time of death, compared with untreated depressed subjects,[10] whereas the brains of depressed patients showed decreased levels of GDNF in limbic areas and basal ganglia.[11] It is interesting that some second-generation antipsychotic drugs, such as olanzapine, also increase BDNF serum levels in schizophrenic patients, generating the idea that these drugs may have a neuroprotective action in the mesolimbic DA system.[12] Based on these findings a plausible hypothesis is that depressed patients with Parkinson disease could have altered BDNF or GDNF levels and that antidepressant drugs may restore them and, potentially, have beneficial effects for depressive as well as parkinsonian symptoms.

With this in mind, the aim of our study was (*a*) to investigate whether depressed patients with Parkinson disease had altered peripheral levels of trophic factors, when compared with nondepressed PD patients and healthy subjects, and (*b*) explore the possibility that antidepressant drugs, in conjunction with antiparkinsonian drugs, may either induce the expression of these factors or significantly modify clinical outcome of depressed patients with Parkinson disease. Thus, we measured by enzyme-linked immunosorbent assay the serum levels of BDNF and GDNF in depressed patients with Parkinson disease, nondepressed patients, and healthy subjects and correlated them with clinical observations.

We included in the study 46 patients with idiopathic PD recruited from the Movement Disorders Clinic of Catholic University of Sacred Heart, Policlinico Gemelli, Rome. Twenty-six of these patients had the diagnosis of major depression disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria, and 15 of them were under antidepressant treatment. Patients were excluded if they had a history of seizures, major head trauma, dementia, previous neurological surgeries, or psychotic symptoms. Patients were also excluded if they were seropositive for HIV or if they had a history of alcohol abuse or dependence and addiction to drugs. Fourteen control subjects individually matched with the PD patients with regard to age, sex, and education level were recruited.

Neurological evaluation of PD patients was conducted during the ON-state and included the Hoehn and Yahr Scale and the Unified Parkinson Disease Rating Scale (UPDRS, motor part III). Depression was diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. All depressed PD patients had a score of at least 16 points at the 21-item Hamilton Rating Scale for Depression.

All patients were treated with levodopa/carbidopa alone or in combination with DA agonists (bromocriptine, selegiline, biperiden, amantadine, and pramipexole). Depressed patients with Parkinson disease also received daily doses of selective serotonin reuptake inhibitors (SSRIs) (50–150 mg/d sertraline, 20 mg/d citalopram, and 20 mg/d paroxetine) according to the medical judgment and psychopathological status.

Venous blood was collected into sampling tubes that were centrifuged within 20 minutes after sampling at 2000*g* for 20 minutes. Serum was then aliquoted and stored at −80°C until analysis. BDNF (cat. N° DY248; R&D Systems) and GDNF (cat. N° G7620; Promega) were detected in sandwich enzyme-linked immunosorbent assays according to the instructions of manufacturers. All assays were performed on F-bottom 96-well plates (Nunc, Wiesbaden, Germany). The detection limits for BDNF and GDNF were 15 pg/mL. Measurements were performed in duplicate, and values are expressed as nanograms per milliliter (BDNF) and picograms per milliliter (GDNF).

Comparisons among the experimental groups (PD patients, depressed patients with Parkinson disease with or without antidepressants, and healthy subjects) on BDNF and GDNF serum levels were performed using univariate analyses of variance followed by Fisher protected least significant difference post hoc test. The χ^2 test was used to compare categorical data. Statistical significance was set at $P < 0.05$.

There were no significant differences in age and sex between PD patients and healthy subjects. Depressed and nondepressed PD patients did not differ in disease duration, disease stage (Hoehn and Yahr Scale), and evaluation of motor (UPDRS III) or mental (Mini Mental State Examination) function. The group of depressed PD patients was characterized by significantly higher scores in depression, melancholia, and pleasure scales and presence of negative symptoms as compared with nondepressed PD patients.

Analysis of variance showed a significant main effect ($P < 0.0001$) for BDNF levels (Fig. 1). Post hoc comparisons showed that PD depressed and nondepressed patients had lower BDNF serum levels as compared with healthy subjects ($P < 0.001$ and $P < 0.05$, respectively). In addition, in PD patients, depression further reduced BDNF as compared with nondepressed PD patients ($P < 0.01$). Vice

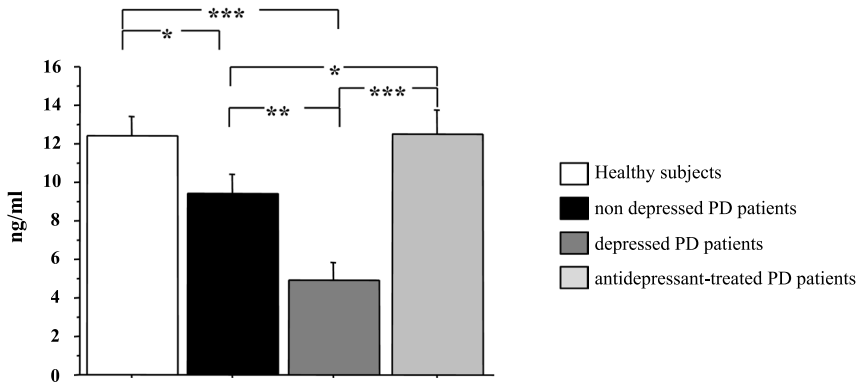

FIGURE 1. Brain-derived neurotrophic factor serum levels in PD patients and healthy subjects. Data are the mean ± SEM. Values are expressed in nanograms per milliliter. Asterisk indicates significant difference between the groups. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

versa treatment with antidepressant drugs restored BDNF to levels similar to those of healthy subjects, as shown in Figure 1.

No significant main effect for GDNF serum levels was observed. Furthermore, post hoc analyses did not reveal significant differences among groups. Depressed patients with Parkinson disease showed GDNF serum levels comparable to those of nondepressed patients. Also, antidepressant treatment did not significantly alter GDNF levels.

Unified Parkinson Disease Rating Scale III values were compared in depressed, nondepressed, and antidepressant-treated PD patients to evaluate the differences in motor function among groups. We found that depressed patients were characterized by a greater deficit in motor function as compared with nondepressed PD patients ($P < 0.01$), but antidepressant treatment reversed this deficit. In fact, antidepressant-treated PD patients showed UPDRS values comparable to those of nondepressed PD patients (see Supplemental Tables 1 to 4, Supplemental Digital Content 1, http://links.lww.com/JCP/A32 and Supplemental Figure 2, Supplemental Digital Content 2, http://links.lww.com/JCP/A33).

Thus, our data indicate that depression can potentially represent an adjunctive worsening factor for PD symptoms and that BDNF is implicated in these events. Indeed, BDNF may have a common role in PD and depression. Decreased levels of BDNF in the substantia nigra pars compacta in postmortem examinations of PD patients have been detected,[13] whereas in depression, a reduced BDNF synthesis has been repeatedly demonstrated in brain regions of humans and animal models.[14,15] Moreover, alteration of different monoaminergic pathways, such as noradrenergic and serotonergic projection, which are defective in depression,[16] has been also reported in PD,[17,18] suggesting that most probably the 2 diseases interact in producing a worsening of clinical state. This hypothesis is somehow supported and revealed by the finding that depressed PD patients, although treated with antiparkinsonian drugs, display a significant worsening of motor function, as measured by UPDRS Scale.

If this is true, then we can assume that a therapeutic approach for depression may also produce beneficial effects on PD and that antidepressant and antiparkinsonian drugs may interact in producing beneficial effects on central nervous system neurons. Supporting this notion, some studies have evidenced that sertraline, an SSRI, is useful for treating depression in PD without aggravating or even improving[19] parkinsonian symptoms, whereas the antiparkinsonian agent, selegiline, exerts neuroprotective effects by modulating BDNF production in selected areas of the mouse brain.[20]

In conclusion, this study indicates that PD patients are characterized by a reduction of BDNF serum levels and that depression may exacerbate this effect and worsen PD symptoms. Given the simultaneous action of BDNF on DA and serotonergic neurons, it is proposed that association between antiparkinsonian treatment and SSRI could be a good therapeutic chance not only for treating depression in PD but also for improving PD symptoms.

AUTHOR DISCLOSURE INFORMATION

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Late-Onset Galactorrhea and Menometrorrhagia With Venlafaxine Use in a Migraine Patient

To the Editors:

Venlafaxine is a dual-effect antidepressant. It is a reuptake inhibitor of both serotonin (5-HT) and norepinephrine.[1] While mainly inhibiting 5-HT reuptake at low doses, at higher doses it also moderately inhibits norepinephrine reuptake, and only at high doses do its slight effects as a dopamine (DA) reuptake inhibitor appear.[1] Venlafaxine is indicated for use in the treatment of psychiatric conditions such as major depression and generalized anxiety disorder. In recent studies, it has also been reported to be effective in migraine prophylaxis.[2,3]

Here a patient is presented whose first year of venlafaxine therapy for migraine prophylaxis resulted in both galactorrhea and menometrorrhagia, a co-occurrence of adverse effects that has not been reported before.

CASE REPORT

The patient was a 36-year-old nurse, married with 2 children ages 10 and 14 years, and her medical and family history was significant only for migraine. Six years earlier, she had received a diagnosis of migraine without aura. Although her migraine attacks at first had occurred 2 to 3 times per month, they had become more frequent in the last 2 years and had begun to occur 6 to 7 times per month. One year ago, for migraine prophylaxis, 150 mg/d of venlafaxine therapy was started. Because of its benefit in reducing the patient's migraine attacks, the drug was continued. In the past 1 month, the patient reported a complaint of galactorrhea occurring without any pain in or enlargement of the breasts. She additionally complained of menstrual irregularities. She said that her period lasted longer than normal and involved a greater amount of bleeding (menometrorrhagia). To investigate these complaints, serum levels of prolactin, follicle-stimulating hormone, luteinizing hormone, progesterone, and estradiol were examined in the follicular phase and were found to be within normal limits. Thyroid hormones were also within normal limits. To look for pituitary pathology, cranial magnetic resonance imaging was done, and findings were normal. Ultrasound investigations of breasts and pelvis also gave normal findings. In the patient's gynecologic, endocrinologic, and breast examinations, no pathological lesion was evident. Because of the possibility that the patient's symptoms were arising from venlafaxine use, the drug was tapered and stopped. The patient's galactorrhea stopped within 2 weeks after cessation of the drug, and the menometrorrhagia stopped within 4 weeks. An objective causality assessment using the Naranjo Probability Scale suggested that venlafaxine was the probable cause of the galactorrhea and menometrorrhagia.[4] (The scale score was 6.)

DISCUSSION

Although the occurrence of galactorrhea secondary to venlafaxine use is very rare, it has been reported in the literature.[5,6] The possibility of menorrhagia and/or menstrual irregularities has also been reported in premarketing and postmarketing data. However, we did not encounter any cases in the literature other than 1 report of amenorrhea occurring after 7 days of venlafaxine use.[7] The present report is the first one in which galactorrhea and menometrorrhagia have been seen together in 1 patient. That these adverse effects were seen so late in the drug's period of use is also an interesting finding.

To explain venlafaxine's capacity to lead to galactorrhea, the drug's effects in inhibiting DA reuptake have been put forward as being responsible.[5,6] It has also been reported that venlafaxine can enhance transmission at postsynaptic 5-HT1A receptors.[7] This increase in 5-HT1A neurotransmission has been proposed as a possible promoter of galactorrhea, having both a direct effect on prolactin release via serotonergic neurons in the hypothalamus and an indirect effect via dopaminergic transmission–mediated inhibition of 5-HT.[4,5,7,8] With venlafaxine used for 3 months in a male patient, serum prolactin and estradiol levels were reported to be higher than normal.[9] That venlafaxine has an effect on DA reuptake at high doses and that this effect is less potent than others are known.[1] However, prolactin levels of our patient were within reference range, and the patient's symptoms improved after discontinuation of medication because serum hormone levels were not reassessed. It is possible that the prolactin level, although in the reference range, was higher than this patient's normal and hence capable of producing pathology.

Given that high doses were not used in the patient reported here, the mechanism of galactorrhea is not known, but a relation to the drug's long-term use is a possibility that may be considered.

The possibility of venlafaxine-associated menometrorrhagia/menorrhagia and other urogenital effects has been reported in premarketing and postmarketing data. As for our patient, after 12 months of venlafaxine use and while continuing the drug, menometrorrhagia occurred. In the subsequent examinations and radiological investigations, no pathological lesion was found. The drug's capacity to cause these types of effects is not completely understood. The emergence of these effects is possibly due to the drug's effects on hormonal modulation. One theory suggests that the pulsatile release of gonadotropin-releasing hormone (GnRH) is regulated by endogenous catecholamines. Norepinephrine is thought to exert stimulatory effects on GnRH, whereas DA is thought to exert an inhibitory effect. Serotonin is believed to affect the menstrual cycle by stimulating luteinizing hormone, prolactin, estradiol, and progesterone secretion,[10] but our patient's hormone levels are all within reference range and serum GnRH levels were not measured.

Another theory suggests that inhibition of the cytochrome P450 system by antidepressants may inhibit metabolism of estrogen and other gonadal steroids, causing changes in ovulation and cycle behavior.[10] However, venlafaxine specifically has minimal P450 inhibitory effects.

In conclusion, to the best of our knowledge, the patient reported here is the first to have developed galactorrhea and menometrorrhagia in association with venlafaxine use. These effects cannot yet be fully explained. The drug's capacity to produce these types of adverse effects may be due to its effects on monoamines, but this is uncertain.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Lamotrigine Effective in Postmenstrual Dysphoric Disorder
A Case Report

To the Editors:

A large body of literature exists regarding the premenstrual dysphoric disorder and its management.[1] However, except for a brief mention about postmenstrual syndrome,[2,3] no detailed studies or case reports pertaining to postmenstrual syndrome and or dysphoric disorder could be traced through MEDLINE search. I am reporting a case of a woman who had symptoms suggestive of typical postmenstrual dysphoric disorder, which partially responded to paroxetine but remitted fully with lamotrigine.

A 19-year-old woman pursuing her graduate course presented in the psychiatric outpatient department with the complaints of nausea, vomiting, epigastric pain, restlessness, irritability, sadness, lethargy, difficulty in concentration, and decreased sleep. The symptoms were cyclic, lasting for 14 to 15 days every month postmenstrually for the last 2 years. The patient hailed from a middle-class affluent family. She had one elder brother and caring parents. She was described to be an introvert, sensitive, obedient, and intelligent woman. Menarche was established at the age of 13 years, and her periods were regular, with normal flow and duration without dysmenorrhea. At the age of 15 years, she started having cyclic distress starting with the onset of menses, crippling her for 14 to 15 days postmenstrually every month. Out of these, the first 4 to 5 days were marked by nausea and vomiting, whereas irritability, sadness, lethargy, and decreased sleep dominated the next 9 to 10 days. Notably, the patient used to be totally asymptomatic during the 14 to 15 days of premenstrual period. The patient had consulted different medical and gynecologic specialists and had been prescribed proton pump inhibitors and hormonal courses without any noticeable relief. The past family and psychosocial history was unremarkable. Mental state examination revealed an anxious, sad, and groaning patient, preoccupied by her nonremitting cyclic distress. Thyroid functions, hormonal profile, and result of endoscopic and ultrasonographic investigations of the abdomen and pelvis were

normal. On the basis of typical cyclic symptoms seen during the postmenstrual phase with full remission during the premenstrual period, normal laboratory test results, and negative physical examination, a diagnosis of postmenstrual dysphoric disorder was made.

After assurance, dietary advice, and psychoeducation, cyproheptadine 4 mg/d (for nausea and vomiting), alprazolam 0.75 mg/d (for anxiety), and fluoxetine 20 mg/d (for depressive symptoms) were prescribed. After 14 days, the patient was asymptomatic, and the same treatment was continued. The next follow-up noted emergence of similar symptoms only during the postmenstrual period. Now fluoxetine was continued; alprazolam was tapered off and replaced by clonazepam 0.5 mg/d. During the third follow-up, symptoms starting with the onset of menses were again noticed. Fluoxetine was tapered off, and medicines such as divalproex sodium 250 mg/d, domperidone 20 mg/d, prochlorperazine 15 mg/d, and imipramine 75 mg/d, were tried alternatively without any relief. During the fifth month, quetiapine 25 mg at bedtime and paroxetine 10 mg twice a day were started. Postmenstrual symptoms decreased during the next 3 cycles to 7 to 10 days but not fully. At this stage, lamotrigine was titrated to 50 mg twice a day for 8 weeks, whereas paroxetine and quetiapine were tapered off. The patient's distress reduced to 1 to 2 days during the next 3 to 4 cycles. Lamotrigine was continued for another 9 months and was then tapered off gradually. At the time of submitting this article, the patient was asymptomatic for 8 months.

Postmenstrually approximately during 14-day period, ovarian follicle development and endometrial growth stimulation occur. The main hormone secreted during this phase is estrogen, and its production depends on various hormones, including gonadotropin-releasing hormone, follicle-stimulating hormone, luteinizing hormone, and inhibin. Gonadotropin-releasing hormone stimulates the production of follicle-stimulating hormone and luteinizing hormone. The rate of production of these pituitary gonadotropins depends on the secretion of estrogen and progesterone from the ovaries, as well as gonadotropin-releasing hormone from the hypothalamus. Therefore, hypothalamic, pituitary, or ovarian dysfunction can all lead to menstrual disorders.[4,5]

The term postmenstrual syndrome, characterized by symptoms of anxiety, defensiveness, indecision, agitated depression, water retention, breast soreness, and others, has been mentioned in 1 newsletter.[2] In this letter, the author has cited estrogen progesterone imbalance translating into elevated tissue zinc-to-copper ratio as one of the etiological explanations for this syndrome. In the present case, the initial postmenstrual distress was characterized by symptoms pertaining to upper gastrointestinal tract (such as nausea, vomiting, and epigastric pain), and this distress was further compounded by another set of symptoms (such as restlessness, irritability, sadness, lethargy, difficulty in concentration, and decreased sleep), which resembled features of agitated depression. Unlike the above-mentioned newsletter,[2] symptoms suggestive of water retention and breast soreness were not seen in the present case; however, depressive and anxiety symptoms were a common finding in both. Also, seeing the nature and severe psychosocial distress associated with these postmenstrual symptoms, a diagnosis of postmenstrual dysphoric disorder seemed more appropriate for this patient. The patient had cyclic symptoms suggestive of agitated depression, which showed marked improvement with lamotrigine therapy. Lamotrigine has been found to be potentially useful in a treatment-resistant menstrually related rapid cycling bipolar II disorder with follicular phase depressive symptoms,[6] which raises a possibility that postmenstrual dysphoric disorder may represent a cyclic variant of a depressive disorder. However, prolonged follow-up of this patient as well as more studies on such patients are needed to know whether this so-called postmenstrual dysphoric disorder is a depressive variant or a separate entity.

The index case not only calls for identifying patients with postmenstrual dysphoric disorder but underlines the effectiveness of lamotrigine in curtailing the distress and disability associated with such disorder.

AUTHOR DISCLOSURE INFORMATION

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A Brief Self-Report Measure to Assess Antidepressant Adherence Among Spanish-Speaking Latinos

To the Editors:

It is important that researchers and clinicians have a practical tool for assessing antidepressant adherence among Latinos. Although low antidepressant adherence is a fairly common occurrence[1] across a range of racial/ethnic groups, it occurs more commonly among racial/ethnic minorities such as Latinos.[2] Low antidepressant adherence is a concern, given that it complicates depression treatment and may be a source of racial/ethnic disparities in depression treatment outcome. Early discontinuation can increase likelihood of depressive relapse by 77%[3] and lead to lower likelihood of achieving full remission, shorter symptom-free periods, and longer time to remission of symptoms.[4] Thus, depression treatment outcomes can be improved by efforts to enhance antidepressant adherence.

The capacity to research and clinically address antidepressant adherence is constricted by the complications of measuring adherence. The most robust adherence measure is perhaps the use of electronic medication container caps, which record the time and date of each bottle opening (eg, Medication Event Monitoring System [MEMS]). Although providing the most precise data, systems, such as MEMS, can increase study and clinical costs and may therefore not always be feasible. Other measures typically used include self-reported discontinuation of medication or dose taking,[2] pharmacy refill data,[1] pill counts,[5] and blood sample

analysis.[5] Each measure for adherence has a different profile of advantages and disadvantages. For example, blood sample analyses place demands on patients and also add to costs. Furthermore, examination of whether an antidepressant was discontinued or refilled provides a limited picture of adherence, as patients may continue their antidepressant but engage in irregular dose taking.

Dimensional self-report measures of adherence have the advantage of providing more information than what can be obtained from a dichotomous indicator. In addition, they are cost-effective and practical to administer, increasing the likelihood that they will be more frequently included in research studies or clinical practice. Such increased measurement of antidepressant adherence would hold promise for better understanding and managing this common problem. However, self-report measures of adherence have the drawback of being influenced by bias. Given their potential benefits, it is therefore necessary to evaluate the validity of self-report measures of adherence against a well-established criterion, such as an electronic medication container. Accordingly, 1 study examined 3 methods of antidepressant adherence assessment (4-item self-report questionnaire, blood analysis, and pill counts), comparing their performance with the MEMS.[5] They found that blood analyses were impractical because of high rates of patient refusal (39%) and that tablet counts overestimated adherence. The authors reported that the 4-item self-report measure (Self-reported Medication Taking Scale [SMTS][6]) was practical to administer and demonstrated a sensitivity/specificity of 72.2% and 74.1%, respectively, for detecting nonadherence.

However, in using the SMTS to study antidepressant adherence among Latinos, there may be concerns about the cultural and linguistic appropriateness of this measure, as the SMTS's psychometric properties have not been examined for antidepressant adherence with Spanish-speaking populations. Given that the SMTS is a practical measure that can be easily included in research studies or as part of standard clinical practice, this letter is to present data on the use of SMTS[5,6] for measuring antidepressant adherence among Spanish-Speaking Latinos. Our study capitalizes on a design where the SMTS was administered, while MEMS data were concurrently collected. The MEMS provides a very suitable criterion by which to examine the SMTS's criterion-related validity, especially in light of recall error and bias concerns. Participants (N = 47) were enrolled in a randomized trial examining an intervention to improve antidepressant adherence. Specifically, participants were receiving outpatient services at a community mental health center and were randomized to receive a motivational adherence intervention or usual care. Given that participants were receiving community mental health center usual care, their psychopharmacological treatment was naturalistic, and therefore, prescriptions varied across individuals. All antidepressants prescribed were as follows: serotonin-norepinephrine reuptake inhibitors (51.1%), selective serotonin reuptake inhibitors (44.7%), or norepinephrine-dopamine reuptake inhibitors (4.3%). Participants were enrolled if they met criteria for major depression or dysthymia within the previous month to baseline (assessed with the Structured Clinical Interview for *DSM-IV*[7]), were being treated with an antidepressant, self-identified as Latino(a), and were of ages 18 to 65 years. Exclusions were made if criteria were met for mania or substance-related disorder within the last year (assessed with Structured Clinical Interview for *DSM-IV*), were medically unstable, or were pregnant/nursing at the time of the study. Nearly all of the participants were predominantly Spanish speaking (89.4%). All research procedures were approved by the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School institutional review board, and all participants signed an approved consent form.

This letter presents data generated from the 4-item SMTS and MEMS. The MEMS was provided to participants at baseline. The SMTS was made specific to antidepressants by replacing the wording in each item from "medicine/medication" to "antidepressant medicine/medication." We then generated a Spanish translation of the measure using a forward/backward translation procedure. The Appendix displays the translated SMTS in its entirety, along with endorsement rates for each item. Respondents indicated "yes/no" to each dose-taking problem represented by the 4 SMTS items, yielding a score of 0 to 4 (higher scores indicate poorer adherence). Our analysis used data from the end-point research evaluation, which occurred 5 weeks after baseline. This allowed a comparison of the end point (5-week) SMTS with the daily adherence data for that 5-week period (MEMS). The MEMS adherence was calculated as the number of days the medication was taken, divided by the total number of days (% of days medication taken).

The percentages of respondents producing different SMTS scores (0–4) were as follows: 0 = 27.7%; 1 = 19.1%; 2 = 21.3%; 3 = 21.3%; and 4 = 10.6%. The SMTS was internally consistent ($\alpha = 0.70$) and demonstrated a moderate negative correlation with MEMS adherence ($r = -0.43$), indicating that more self-reported dose-taking problems were associated with lower adherence. For each score on the SMTS, the mean MEMS adherence rate was as follows: 0 = 74.1% (SD, 12); 1 = 70.9% (SD, 36.59); 2 = 60.2% (SD, 30.16); 3 = 44.1% (SD, 44.06); and 4 = 23.4% (SD, 39.27). An omnibus test indicated that these means were significantly different ($F = 2.80$; $P < 0.05$).

Next, to maximize comparability between studies, we chose an MEMS adherence criterion that is commonly used in studies to identify the adherent participants (≥80%) and examined different SMTS cutoffs (Table 1).[5,8] Using the cutoff proposed by George et al,[5] an SMTS score of 1 or more yielded a sensitivity and specificity of 45% and 85.2%, respectively, for identifying adherent participants. However, improved classification was demonstrated with an SMTS cutoff of 2 or more. Specifically, endorsing 2 or more items on the SMTS demonstrated a sensitivity and specificity of 70% and 70.4%, respectively, which amounted to a total classification accuracy of 70.2%. Given that the respondents were in

TABLE 1. Sensitivity/Specificity of SMTS Cutoffs for Identifying 80% or Greater MEMS Adherence

	Nonadherent (MEMS, <80%)	Adherent (MEMS, ≥80%)
SMTS 1+ cutoff		
SMTS = 1–4	23 (85.2%)	11 (55%)
SMTS = 0	4 (14.8%)	9 (45%)
SMTS 2+ cutoff		
SMTS = 2–4	19 (70.4%)	6 (30%)
SMTS = 0–1	8 (29.6%)	14 (70%)

Figures represent frequencies. Percentages reflect the proportion within column.

different adherence conditions (ie, usual care vs motivational intervention) and were receiving different antidepressant prescriptions, a logistic regression examined whether the relationship between the SMTS cutoff of 2 or greater and MEMS (≥80%) was confounded by receiving the intervention or antidepressant class.Participants with an SMTS score of 2 or higher remained 83% less likely to have MEMS adherence of 80% or more, after adjusting for intervention condition and antidepressant class (odds ratio, 0.17; 95% confidence interval, [0.04–0.77]; $P < 0.05$). The covariates were not significant ($P > 0.05$).

DISCUSSION

These results describe the performance of a brief self-report measure to assess antidepressant adherence among Spanish-speaking Latinos. The SMTS demonstrated acceptable reliability and was statistically and meaningfully related to a robust adherence criterion (MEMS). With each increase in SMTS score, a corresponding decrease in mean MEMS adherence was observed. Our sensitivity/specificity analysis showed that an SMTS cutoff of 2 or more was the most appropriate. This finding diverged from that of a previous study, and the reason for this is not clear.[5] One explanation would pertain to cultural differences. As a possible example, there may be culturally influenced differences in a duteous style of reporting adherence problems. The divergent finding also may be related to language differences. However, given the very few English-speaking Latino participants, our data cannot differentiate whether the divergent findings were more related to language or culture. The diverging findings regarding cutoff also could be related to generalizability problems related to the relatively small samples. For this reason, the current results should be studied further to determine the best SMTS cutoff for case finding.

The SMTS's performance in the current study is noteworthy, given how practical and feasible this measure is to administer clinically or in a research protocol. Other more involved methods (pharmacy data, pill counts, and use of the MEMS) may indeed yield more robust data. However, for the studies that require less involved or less costly assessment of adherence among Spanish-speaking Latinos, the current results show that the SMTS moderately corresponded with MEMS adherence. In addition, the total classification accuracy of 70.2% seems very similar to the SMTS estimate (73%)[5] generated for antidepressant adherence with a mostly English-speaking, non-Latino white population in the United Kingdom (written communication, March 2010).

Given the limited sample size, generalizability is likely limited, and future studies should seek to replicate these results. In addition, the current study was limited by the lack of a comparison group (either English-speaking Latinos or other racial/ethnic groups) for determining if there are between-group differences with regard to the SMTS's psychometrics.

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APPENDIX

Self-Reported Medication Taking Scale

Item	Response	MEMS Adherence, ≥80%	MEMS Adherence, <80%
1. Do you ever forget to take your antidepressant medicine? *¿Alguna vez se ha olvidado de tomar su medicina anti-depresiva?*	Yes/No	11 (55%)	19 (70%)
2. Are you careless at times about taking your antidepressant medicine? *¿Algunas veces, eres descuidada(o) en tomar su medicina antidepresiva?*	Yes/No	5 (25%)	17 (63%)
3. When you feel better, do you sometimes stop taking your antidepressant medicine? *¿Cuando se siente mejor, algunas veces ha dejado de tomar su medicina anti-depresiva?*	Yes/No	4 (20%)	14 (51.9%)
4. Sometimes if you feel worse when you take the antidepressant medicine, do you stop taking it? *¿A veces, si se siente peor cuando se toma su medicina anti-depresiva, deja de tomarsela?*	Yes/No	1 (5%)	8 (29.6%)

Figures represent the frequency (percentage) who endorsed "yes" on each item, separately by 80% MEMS criterion.

Delayed-Onset Mirtazapine-Related Leukopenia and Rechallenge

To the Editors:

Most cases of drug-related leukopenia develop within the first few weeks of treatment; however, delayed-onset drug-related leukopenia has also been reported, including that with psychotropic medications.[1,2] Mirtazapine is reported to be associated with leukopenia, neutropenia, and agranulocytosis.[3] We present a case of leukopenia in a patient treated with mirtazapine for dysthymia and posttraumatic stress disorder, which was found only after extended treatment with the agent. After drug discontinuation and unsuccessful treatment with 3 other antidepressants, the patient has tolerated rechallenge with a lower dose of mirtazapine.

CASE REPORT

Our case patient, a 41-year-old woman, had presented to the hospital clinic with symptoms of depressed mood, poor energy, irritability, flashbacks, and nightmares of her mother's homicide. She met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for dysthymia and posttraumatic stress disorder. After being stable on mirtazapine at 45 mg/d at bedtime and quetiapine at 50 mg/d at bedtime for 5 years (both off-label use), the patient was diagnosed with asymptomatic moderate leukopenia on routine medical workup, with white blood cell (WBC) count, 3900/μL (reference range, 4800–10,800/μL);[4] neutrophils, 39% (reference range, 50%–75%); and absolute neutrophil count (ANC), 1900/μL (reference range, 2500–7500/μL); other cell components were within the reference range. Mirtazapine was discontinued, and within 2 weeks, her WBC count returned to normal (5000/μL; neutrophils, 55%; ANC, 2800/μL). She was later switched sequentially to fluoxetine, escitalopram, and paroxetine, each of which was discontinued owing to adverse effects and/or nonresponse but with no evidence of leukopenia. Quetiapine at 50 mg/d at bedtime was continued throughout (no serum levels for quetiapine or mirtazapine were obtained). Owing to persistent clinical symptoms, the patient was restarted on mirtazapine approximately 18 months after the medication was initially discontinued, and the dose was gradually increased to 30 mg/d at bedtime. For the past 2 years, she has clinically improved on 30 mg of mirtazapine daily and 50 mg of quetiapine daily at bedtime, with no adverse effects, and is monitored regularly for hematological problems. Her ANC level has remained in the lower reference range (2200–2800/μL) since rechallenge and never reached her prior nadir of 1900/μL or followed a consistent suppressed pattern, nor have clinical leukopenic manifestations emerged. The patient's medical history was negative for any endocrine or hematologic problems or other medical conditions that would predispose to leukopenia.

DISCUSSION

In premarketing trials, the incidence of agranulocytosis/severe leukopenia with mirtazapine was 1.1 in 1000 subjects.[5] Since its introduction in 1996, less than 10 cases of mirtazapine-related leukopenia/neutropenia, including with concomitant medication, have been reported. Our patient's clinical course is consistent with her developing delayed-onset leukopenia as a consequence of prolonged treatment for 5 years. The patient had no documented history of illnesses suggestive of previous leukopenia, and her prior routine laboratory monitoring had not identified any neutropenic trends as per the patient. According to the Naranjo probability scale,[6] mirtazapine can be postulated to have caused our patient's leukopenia with intermediate probability. Whereas the sequence of events and the lack of other risk factors suggest that mirtazapine was associated with the leukopenia, the effect may be unrelated to mirtazapine, accounted for by other explanations such as idiopathic leukopenia with genetic vulnerability or cyclic leukopenia. It is also possible that leukopenia was facilitated by concurrent quetiapine.

The mechanisms of leukopenia with mirtazapine therapy are not well understood. Hypersensitivity/immune-mediated mechanisms have been suggested, including complement-mediated toxicity[7] and drug-induced antibodies against committed stem cells, proliferating precursors, or mature blood cells.[8,9] Long-term administration of the drug may result in haptenation and accelerated apoptosis.[10] The current tolerated rechallenge at a moderately reduced dose of 30 mg of mirtazapine suggests that even with evidence of mirtazapine-related leukopenia, subsequent use of the drug in clinically indicated settings can be considered. In the absence of guidelines for managing hematologic adverse effects of psychotropic agents other than for clozapine, especially considering the risk of late emergence of the adverse effect, long-term hematologic monitoring of patients such as ours seems indicated.

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Behavioral Disinhibition With Baclofen

To the Editors:

Prevention of relapse is considered the major challenge in the treatment of alcohol dependency. Baclofen, a GABA-B agonist, has recently demonstrated efficiency to reduce consumption and enhance abstinence in animal models of alcoholism and alcohol-dependent patients.[1–5] We report a case of baclofen-related disinhibition.

CASE REPORT

Mr A, a well-known physician and academic, is a 66-year-old white man with a long history of alcohol consumption. He started abusing alcohol at a young age in festal settings, but shortly after, he began drinking abusively at home alone. Since a few years, he was drinking a bottle of vodka each night after work. Several hospitalizations took place in the last couple of years, with an early relapse soon after discharge except for 10 months of abstinence with a daily dose of disulfiram. No personality disorder was found on psychometric tests, and no mood disorder or anxiety disorder preceded or complicated his dependency. On April 2009, he was admitted, again, in the protected unit of our department, brought by his family and the police for alcohol abuse. On admission, he was agitated, easily irritable, and aggressive with a blood alcohol level of 2.8 g/L. A treatment with diazepam, 30 mg/d, was started. The next day, a psychiatric evaluation was performed, and the diagnosis of alcohol dependency with no other psychiatric comorbidity was made. The alcohol withdrawal phase occurred without any complication except for a state of disinhibition, which he had previously presented in the same settings, characterized by irritability, psychomotor agitation, and verbal aggressiveness. This state was identical to the one he frequently presents after alcohol ingestion and reminded us of his clinical state on admission.

At the ending of the withdrawal phase, and to enhance this patient's abstinence, a treatment with 20 mg/d of baclofen was initiated. At day 5, the dose was increased to 40 mg/d, and at day 7 to 60 mg/d, to achieve a high but safe daily dose of baclofen, as recently suggested for the treatment of alcoholism.[6] At this dose, the patient became disinhibited, easily irritable, and verbally and physically aggressive. No signs of confusion, awareness disturbance, spatial or temporal disorientation, lethargy, or myoclonus were found. His state was very similar to the one he usually presents under alcohol or benzodiazepine. The 60 mg/d of baclofen was maintained. The next day, in the same state of disinhibition, the patient took advantage of a nurse trainee opening the door of the unit to shove her violently, throwing her to the floor, and run away. He returned, 3 days later, brought again by his family. He had stopped his medication throughout this period. Upon his return, he was very calm, criticizing with regrets and astonishment his previous conduct. In the presence of these recurrent episodes of disinhibition, a diagnostic reevaluation was performed, looking for possible explanations for this substance-induced behavioral disorder. No personality disorder was again found, a result supported by the high social and professional functioning and performance of the patient. No mood disorder, anxiety disorder, cognitive deterioration, or other psychiatric disorder was found. No cortical atrophy or subcortical lesion was found on cerebral magnetic resonance imaging. A cerebral perfusion scintigraphy, using the 99mEC-ECD marker, was done. It showed a bilateral hypoperfusion of the internal temporal structures and a mild hypoperfusion of the left temporal parietal associative cortex and the mesial frontal region. An electroencephalogram (EEG) was done and showed no abnormality. In the absence of an organic etiology for these episodes of disinhibition, including encephalopathy, baclofen was then restarted at the dose of 10 mg/d. Five days later, the patient was mildly disinhibited and euphoric. The EEG showed intermittent left temporal and parietal subcortical puffs of delta waves, lasting from 1 to 3 seconds with no signs of encephalopathy. In the absence of any metabolic disturbances, these findings were attributed to baclofen. This drug was then stopped. Eight days later, the EEG was normal again, and the patient's disinhibition had disappeared.

DISCUSSION

Behavioral disinhibition occurring secondary to benzodiazepine intake is known and has been frequently reported.[7] A plausible explanation of this GABA-A agonist–related paradoxical effect is an increased metabolism in previously dysfunctional mesioprefrontal-striatal loops.[8,9] This hypothesis is in line with other reported studies on GABAergic drugs, including papers on zolpidem, a selective GABA-A $\alpha 1$ subunit receptor agonist. Zolpidem has shown clinical improvement in patients with Broca's aphasia following subcortical and striatal lesions. This improvement was associated to an increased metabolism of the mesial frontal and orbitofrontal cortexes.[10] Amelioration of behavioral disinhibition in schizophrenic patients associated to an increase in the metabolism of the mesial frontal cortex has also been documented,[8] as has its efficiency in the treatment of catatonia.[11] In the latter condition, abnormal activations of mesial frontal and orbitofrontal cortex have been demonstrated[12] and are corrected by lorazepam,[13] demonstrating both dysfunctional mesioprefrontal-striatal loops and potential benefits of benzodiazepines. A similar phenomenon, behavioral disinhibition, occurring with GABA-B agonists has never been reported so far and was observed here in a patient presenting mesioprefrontal hypoperfusion. According to the Naranjo probability scale, return to the basal clinical state on drug discontinuation and then reappearance on rechallenge argue for a baclofen causal role in this disinhibition.[14] Encephalopathy with EEG perturbations, that is, periodic sharp wave pattern, quasi-periodic generalized epileptiform discharges, generalized bursts of sharp wave discharges, or burst-suppression pattern, has been described in baclofen-treated patients, especially with intrathecal administration.[15] Nevertheless, in the case of our patient, none of the previously described perturbations was found. Baclofen administration resulted in delta waves originating from structures showing hypoperfusion on scintigraphy, and most important, our findings were associated to a clinical state characterized by disinhibition and impulsivity in the total absence of confusion, disorientation, sedation, or any other sign in favor of a baclofen-related encephalopathy.

Therefore, this case report expands paradoxical reactions to all GABAergic drugs, including GABA B medication, and reinforces the hypothesis of a functional deficiency in the mesioprefronto-striatal loops underlying behavioral disinhibition. Psychiatrists should be aware of this potential adverse drug reaction in the light of the growing prescription of baclofen.

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