Use of Antacid Medication in Patients Receiving Clozapine
A Comparison With Other Second-Generation Antipsychotics

To the Editors:

Dyspeptic complaints seem to be highly prevalent in chronic psychiatric patients, particularly those taking clozapine.[1] Clozapine has also been reported to be temporally associated with the emergence of reflux esophagitis[2,3] and an increased use of antacid medication.[4] Despite this, large-scale effectiveness studies have not reported increased rates of antacid prescribing in clozapine-treated cohorts relative to those on other atypical drugs.[5] To date, no study has attempted to establish the comparative prevalence of antacid use in those taking clozapine and those receiving other second-generation antipsychotics (SGAs). One of the reasons for this is that clozapine is dispensed only by discrete hospital pharmacies, a practice that precludes large-scale analysis of prescribing practice using computer databases.

During 2009, we identified all community (ie, discharged) patients receiving SGA medication from Lambeth and Maudsley hospital pharmacy departments in southeast London. For each patient, we established sex, ethnicity, age, and prescribed medication. Data were derived from electronic case notes and prescription charts and by contacting general practitioners when necessary.

We compared the prevalence of antacid use (proton-pump inhibitors [PPIs], H2 antagonists, and other antacids (alginates, magnesium trisilicate, misoprostol) in those receiving clozapine with patients receiving nonclozapine SGAs by establishing crude odds ratio (OR) and OR adjusted for statistically significant ($P < 0.05$) confounding variables (ie, those shown to be associated with antacid prescribing). To do this, we first constructed a univariate logistic regression model and then established a final multivariable model (using SAS Enterprise Guide version 3.0, SAS Institute Inc, Cary, NC).

The characteristics of the 2 study groups are shown in Table 1. Mean dose of clozapine was 423 (SD, 162) mg/d (range, 70–1000 mg/d). Mean duration of treatment with clozapine was 393 (SD, 256) weeks (range, 15–994 weeks). In the nonclozapine group, 155 patients (43%) received olanzapine as the principal antipsychotic, 80 (22%) risperidone, 64 (18%) aripiprazole, 41 (11%) quetiapine, 23 (6%) amisulpride, and 1 patient (0.3%) received ziprasidone.

In the clozapine group, 45 patients were prescribed PPIs (13.1%), 7 (2.0%) H2 antagonists, and 12 (3.5%) were prescribed

TABLE 1. Patient Characteristics and Prescriptions

	Clozapine (n = 343)		Nonclozapine (n = 364)		Statistics		
Characteristic*	**n**	**%**	**n**	**%**	χ^2	*df*	*P*
Male sex, n	246	71.7	217	59.6	11.449	1	0.001
Ethnicity					32.812	3	<0.001
White	156	45.6	97	26.7			
Black	147	43.0	221	60.9			
Asian	19	5.6	12	3.3			
Other	20	5.8	33	9.1			
Age, y	43.0*	64[†]	42.0*	54[†]	−1.557[‡]		0.119
Psychiatric cotherapies							
Antipsychotic	95	27.7	23	6.3	58.044	1	<0.001
Mood stabilizers	54	15.7	48	13.2	0.935	1	0.334
Antidepressants					8.892	3	0.031
SSRI	67	19.5	59	16.2			
Tricyclic antidepressants	12	3.5	5	1.4			
Other	10	2.9	23	6.3			
Benzodiazepines	30	8.7	22	6.0	1.893	1	0.169
Other medication							
Laxatives	45	13.1	5	1.4	37.073	1	<0.001
Antimuscarinic agents	134	39.1	29	8.0	96.283	1	<0.001
Antimotility agents	3	0.9	8	2.2	2.019	1	0.155
Nonsteroidal anti-inflammatory drugs	15	4.4	15	4.1	0.028	1	0.868
Corticosteroids	15	4.4	5	1.4	5.780	1	0.016
Other "high-risk" drugs[§]	28	8.16	16	4.40	4.2953	1	0.0382

*Median.

[†]Range.

[‡]Wilcoxon-Mann-Whitney.

[§]High-risk drugs included calcium antagonists and β-agonists (known to be associated with dyspepsia).

other antacids. In the nonclozapine group, 9 (2.2%) were prescribed PPIs, 1 (0.3%) an H2 antagonist, and 5 (1.4%) were prescribed other antacids. Crude OR for receiving any antacid medication (clozapine, 18.6%; nonclozapine, 3.9%) was 5.2 (95% confidence interval, 2.8-9.6; $P < 0.0001$).

In the final multivariable model, use of antacids was associated with age ($P = 0.008$), prescription of a second antipsychotic ($P = 0.039$), laxative prescription ($P = 0.0002$), nonsteroidal anti-inflammatory drug prescription ($P = 0.0003$), and corticosteroid prescription ($P = 0.0001$). Gastroesophageal reflux is generally more common in whites[6] (who were overrepresented in the clozapine group), but ethnicity did not significantly influence frequency of use of antacids in our samples. No other factor was significantly associated with prescription of antacids. Accounting for confounders produced an adjusted OR of 3.4 (95% confidence interval, 1.7–6.8; $P = 0.0005$).

Thus, antacid prescription was significantly more prevalent in patients receiving clozapine than in those receiving nonclozapine SGAs. This observation extends our understanding of the previously reported association of clozapine with upper gastrointestinal symptoms.[1–4]

The reasons for increased prescribing of antacids in people taking clozapine are not clear. Clozapine seems to reduce gastric acid secretion[7] but has been reported to induce gastric outlet obstruction[8] and to impair esophageal function.[9] This impairment of esophageal peristalsis may be the cause of the frequently observed sialorrhea seen in people receiving clozapine.[10] The high use of anticholinergic agents to treat clozapine-associated sialorrhea (39.1% of subjects in this study) may also contribute to esophageal dysfunction: anticholinergic drugs have been linked to esophageal atony.[11]

Limitations of our method include the cross-sectional nature of data capture (thus making causation difficult to establish), that we did not account for some possible confounding variables that were not reliably recorded in our data sources (eg, smoking status), and that we did not clearly establish the reasons for antacid prescribing.

There are 3 important clinical implications of our findings: antacids seem to be frequently required in people taking clozapine, so clinicians should be aware of the increased likelihood of emergent upper gastrointestinal symptoms in these patients; the potential for interaction should be considered because omeprazole may reduce clozapine plasma levels[12]; and our findings suggest a possible link between the risk of fatal pneumonia in people prescribed clozapine[13] and the association of PPI use with an increased risk of pneumonia.[14]

In this cohort, antacid use was much more prevalent in those prescribed clozapine than in those prescribed other SGAs. It is likely that it was a result of an increased rate of gastroesophageal reflux symptoms in people taking clozapine.

AUTHOR DISCLOSURE INFORMATION

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Clozapine Is Cytotoxic to Primary Cultures of Human Bone Marrow Mesenchymal Stromal Cells

To the Editors:

Clozapine is one of the most effective antipsychotic drugs, but its use is limited by a high incidence of agranulocytosis in 0.8% of patients.[1] The molecular mechanisms of clozapine-induced agranulocytosis are still poorly understood. Clozapine does not exhibit direct toxic effects to peripheral or progenitor blood cells at therapeutic concentrations.[1] Nevertheless, when clozapine is bioactivated (oxidized) to a nitrenium ion, it will induce neutrophil apoptosis at therapeutic levels.[2,3] Most of the research regarding the mechanisms of agranulocytosis has focused on its effects on various hematopoietic cells. A recent

report, however, demonstrated that bioactivated clozapine induced cell death in immortalized stromal cell lines, whereas clozapine without bioactivation was not cytotoxic.[4] Mesenchymal stromal cells (MSCs) are a nonhematopoietic stem cell population endowed with the capacity to generate osteoblasts, chondrocytes, adipocytes, and cells that regulate hematopoiesis.[5] The stroma provides a specialized microenvironment for hematopoiesis that supports granulopoiesis and the development of other hematopoietic precursor cells.[4–6] As toxicity of clozapine has been demonstrated in immortalized stromal cell lines,[4] we investigated whether similar effects are seen on primary cultures of human bone MSCs. We exposed MSCs to clozapine and its reactive metabolites that were generated by oxidation with horse radish peroxidase (HRP)–H_2O_2.[1,4]

Mesenchymal stromal cells were obtained from heparinized bone marrow aspirates of 5 healthy male volunteer donors, aged 21 to 29 years old, and one was 72 years old. The donors gave their written informed consent, and the study was approved by the ethics committee of Helsinki University Central Hospital, Finland. A previously described procedure was used to isolate the MSCs.[7] The detailed cell culture procedure can be obtained from the authors. The multilineage potential of the MSCs was tested by their ability to differentiate into osteoblasts and adipocytes as described.[5] Mesenchymal stromal cells from passages 4 to 5 and human fibroblast passages 8 and 17 were used for the experiments. The MSCs and the human fibroblasts were incubated with clozapine at a concentration of 10 μmol/L in the absence or presence of the oxidation system. Altogether, 3 U HRP/20,000 cells in a total volume of 100 μL in a 96-well cell culture plate were added, and the reaction started with 25 μmol/L H_2O_2, both diluted in phosphate-buffered saline as described.[1,4] Suitable concentrations of HRP and H_2O_2 for subsequent assays were determined in preliminary experiments (data not shown). The plates were incubated at 37°C and 5% CO_2 in air for 24 hours. The experiments were performed using 3 to 5 parallel wells per condition and the adenosine triphosphate (ATP) luciferase assay used to detect the cytotoxicity of the cell cultures. The assay procedure can be obtained from the authors upon request. The values given for stromal cells in the experiment comparing MSCs and human fibroblasts were the mean (SD) of 4 separate experiments and, for human fibroblasts, the mean (SD) of 3 experiments. The results of the individual experiments were combined and normalized to the values of the control MSCs and fibroblasts that were taken as 100%. The values comparing the effect of the bioactivation system were the mean of 2 experiments for MSCs and 1 experiment for human fibroblasts. The differences in means were analyzed by Student 2-tailed *t* test (2-sample equal variance), and statistical difference was compared with untreated cells as controls. A $P < 0.05$ was considered to indicate significance.

Mesenchymal stromal cells and fibroblasts were incubated with 10 μmol/L of clozapine for 24 hours, and cell viability was measured with the ATP luciferase assay. The MSCs were very sensitive ($P < 0.05$) to the toxic effects of 10 μmol/L clozapine (Fig. 1).

Interestingly, clozapine was not toxic to fibroblasts but rather appeared to stimulate their growth ($P = 0.006$). Moreover, unmodified clozapine at a concentration of 10 μmol/L was toxic to MSCs, whereas bioactivation with HRP + H_2O_2 nullified this toxicity. The difference was significant between untreated and clozapine-treated cells in the absence of bioactivation ($P = 0.006$). Treatment of MSCs with the oxidation system alone did not induce cytotoxic reaction ($P = 0.22$). Interestingly, oxidation counteracted the toxicity of clozapine because the difference between untreated cells and cells treated with bioactivated clozapine was not significant ($P = 0.50$). Clozapine (10 μmol/L) with or without bioactivation had no toxic effect on the fibroblasts. Without bioactivation, clozapine had a growth-stimulatory effect as compared with control cultures ($P = 0.03$). Bioactivation of clozapine seemed to cancel its growth-stimulatory effect on fibroblasts. Bioactivation alone stimulated fibroblast growth, but this effect nearly disappeared in combination with clozapine.

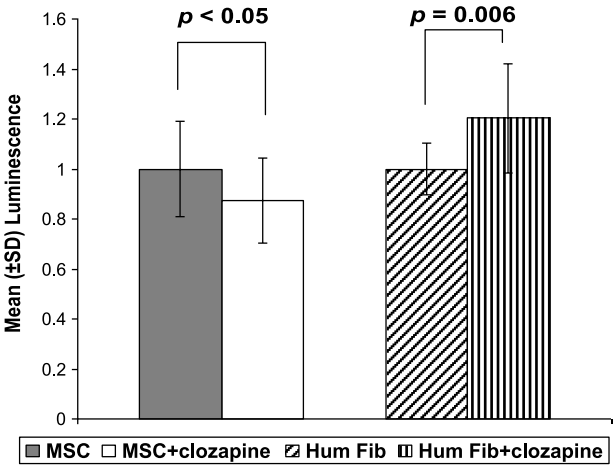

FIGURE 1. The effect of 10 μmol/L of clozapine on cultures of mesenchymal stromal cells (MSC) and of skin fibroblasts (Hum Fib). The cells were treated for 24 hours, and ATP content was measured by quantitative bioluminescence. The mean values (SD) are shown. The statistical differences between untreated cells and cells treated with clozapine are indicated.

DISCUSSION

Our results demonstrate that clozapine is cytotoxic to primary MSCs. Although bioactivation of clozapine has been claimed to play an important role in the development of clozapine-induced agranulocytosis, we were unable to find any additional toxicity of 10 μmol/L of bioactivated clozapine to primary bone MSCs. Our finding is supported by a study of Gardner et al[3] who reported that clozapine adducts did not induce myelotoxicity in rat bone marrow. The present findings differ from those of the study using immortalized human bone marrow MSC line, where clozapine was cytotoxic only after bioactivation.[4]

Clozapine-induced neutropenia and agranulocytosis may have different etiological mechanisms.[8] Milder cases of white blood cell dyscrasia may represent increased sensitivity to the reactive metabolite.[9] The more serious conditions and the fatal cases often occurring within the first 3 months of treatment may indicate a direct cytotoxicity toward the bone marrow MSCs. We were able to show toxic reaction toward mesenchymal stromal cells at a clozapine concentration of 10 μmol/L, which is slightly supratherapeutic, as 1 to 3 μmol/L corresponds to therapeutic levels in vivo.[2] Clozapine treatment typically extends from months to years. We hypothesize that the modest growth-inhibitory effects that we detected may be amplified in the bone

marrow of patients undergoing long-term therapy with clozapine. Mesenchymal stromal cells and fibroblasts could metabolize clozapine along different pathways and therefore accumulate toxic compounds differently. An alternative explanation could be that the uptake of clozapine by primary mesenchymal stromal cells may be more efficient.[10]

Our study has several limitations. The results are based on a small number of experiments, and also, there was considerable variation in the luminescence emitted by both cell types possibly reflecting the special nature of primary MSCs. Moreover, the MSCs of individual donors may differ in their sensitivity to clozapine, which could influence the results. We incubated the cells with clozapine for only 24 hours. The modest growth-inhibiting effects detected may be amplified in the bone marrow of patients undergoing long-term therapy with clozapine lasting typically months or even years. In addition, the onset of agranulocytosis is delayed. Furthermore, we did not study the effect of other atypical antipsychotics on bone marrow MSCs, and it is therefore not known whether stromal cell cytotoxic reaction is unique to clozapine.

In summary, we have demonstrated the specific sensitivity of cultured mesenchymal stromal cells to clozapine. Our results indicate that a direct cytotoxic effect on bone marrow MSCs is one possible mechanism by which clozapine induces agranulocytosis.

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Severe Bowel Ischemia Due to Clozapine With Complete Remission After Withdrawal

To the Editors:

Clozapine is a very efficient atypical antipsychotic whose use has decreased because of the risk of neutropenia and agranulocytosis, which makes clinical management complicated because of the need for hematologic monitoring.[1] However, clozapine has proven to be more effective than other antipsychotic drugs against treatment-resistant schizophrenia and the negative symptoms of schizophrenia.[2] The effectiveness of clozapine could be due to its dual action on serotonin and dopamine receptors; however, this same action could be responsible for the increased frequency of gastrointestinal effects related to hypomotility, including mild effects such as persistent constipation, and more severe effects, such as fecaloma, paralytic ileus, or, more rarely, very severe perfusion impairment leading to bowel ischemia and death.[3]

CASE REPORT

Our patient was a 34-year-old unemployed white male living with his parents in a small town on the outskirts of a large city in the center of Spain. Some months before the current episode, he had to quit his job as a systems engineer because of the severity of his symptoms. He had been diagnosed with paranoid schizophrenia 2 years earlier, and since then, he has been admitted to our psychiatric inpatient unit 4 times after suicide attempts (overdose of different antipsychotics and benzodiazepines in each case). During the same period, the patient also had to be hospitalized in our day unit. His schizophrenia was refractory to long-term treatment with different antipsychotics (olanzapine 20 mg/d, risperidone 4.5 mg/d, ziprasidone 120 mg/d), with a predominance of negative symptoms and progressive impairment. The patient was started on clozapine with a progressive increase in dosage to a maximum of 200 mg/d in the following 3 months until the current episode. No other antipsychotic drugs were administered during this period.

During his most recent hospital stay (November 2008) and after an episode of constipation lasting several days, the patient developed acute abdominal pain, hypotension, and hematemesis and had to be admitted to the general emergency room because of hemodynamic instability. An abdominal radiograph showed marked

dilatation of intestinal loops, which computed tomography identified as a giant fecaloma with secondary dilatation of the gastrointestinal tract, pneumatosis of the intestinal wall, and air in the portal vein.

An exploratory laparotomy was performed to assess potential fecal impaction in the sigmoid colon. This was confirmed, as was the presence of inflammatory fluid in the peritoneal cavity. The fecaloma was then extracted through the anus, and the patient was transferred to the recovery unit. During his stay in this unit, he remained hemodynamically unstable with coagulopathy (international normalized ratio, 2.17), fever, and bilateral pleural effusion, all of which pointed to a diagnosis of septic shock. During the 10-day stay in the recovery unit, the patient's progress was favorable, although diarrhea with negative stool cultures and colonic edema persisted, thus suggesting colitis.

After 10 days, the patient was admitted to the general surgery ward, where his symptoms had a torpid progression with bloody diarrhea, low-grade fever, abdominal pain, vomiting, general discomfort, and cachexia. He again experienced hemodynamic decompensation and several episodes of delirium. After 2 weeks in the general surgery ward, colonoscopy revealed intense mucosal inflammation, extensive ulceration, and spontaneous bleeding. A series of biopsies suggested the diagnosis of ischemic colitis. The pathology report revealed mucosal involvement with mild chronic inflammation and fibrinous-necrotic ulcers and granulation tissue, without specific inflammatory signs or neoplastic elements.

Given the poor outcome of the acute intestinal pain, persistent diarrhea, vomiting, cachectic state, and hemodynamic instability, a second colonoscopy was performed 2 weeks after the first one and revealed increased size of the ulcers, with persistent bleeding. Additional surgery to remove the affected segment was planned by surgeons in case the patient's condition did not improve. After screening for potential causes of ischemic colitis, clozapine was considered a possible causal agent. After an exhaustive review of the patient's records and the literature, the psychiatric consultation-liaison service recommended replacing clozapine with haloperidol (3 mg/d).

During the 2 weeks after clozapine was withdrawn, the patient's intestinal symptoms progressed favorably to an almost complete recovery; the diarrhea disappeared, and the patient's general situation improved. No positive psychotic symptoms were detected, and he was discharged from hospital with no need for further surgery.

Two months after discharge, the patient had gained almost 10 kg in weight and had a healthy general appearance with no further intestinal complications. He was also psychologically stable.

DISCUSSION

The hematologic[1] and cardiac effects[4] of clozapine are very well known and are taken into account in the clinical management of this drug.[1,5] However, severe gastrointestinal effects have received less attention and do not appear in clinical guidelines for clozapine.[6] It is well known that between 14% and 60% of patients on clozapine present with constipation,[3,7] but it is not as well known that clozapine can also produce other motility disturbances such as dysphagia,[3] ileus,[8] intestinal obstruction,[9] megacolon,[3] and even ischemic colitis.[10,11] Severe gastrointestinal effects appear during the first year of treatment in 50% of cases, and the period with the greatest risk is during the first 4 months (30%).[3] In a recent review, 28% of severe intestinal effects were fatal.[3,9]

Hypomotility has been related to clozapine's anticholinergic effect, but this effect per se cannot explain the greater prevalence of these effects with clozapine than with other neuroleptics that have a similar anticholinergic effect; therefore, hypomotility could be related to 5-HT3 antagonism,[3] which would induce slower colonic transit, reduced gastrocolonic reflex, increase in colonic distensibility, and probable reduced sensitivity to distension.[12] The most common symptoms are abdominal pain, abdominal distension, vomiting, diarrhea, and septic shock (in 32% of cases).[3]

Severe gastrointestinal effects related to hypomotility could be explained by several pathophysiological processes, such as untreated intestinal obstruction or pseudoobstruction, which can induce necrosis, distension, perforation, and sepsis. In addition, an impacted fecaloma can increase intraluminal pressure, thus reducing perfusion and leading to ischemia. When necrosis is already present, the mortality rate is about 50%. It may be accompanied by infection secondary to fecal stasis, which can produce secondary bacterial proliferation.[3] Some drugs can induce intestinal ischemia by directly disturbing perfusion in the colonic mucosa.[13] All these mechanisms could have played a role in our case, where the patient initially presented fecaloma, with subsequent progress to sepsis and intestinal ischemia.

Severe hypomotility-related intestinal effects have been reported to revert after withdrawal of clozapine[14]; however, as far as we know, patients whose intestinal involvement progressed to ischemic colitis required extensive intestinal resection or died.[11] The favorable outcome of our patient after withdrawal makes the case particularly interesting, because it shows the importance of an early diagnosis of hypomotility effects related to clozapine to avoid progression to severe complications, with increased risk and much more difficult management.

We think that clozapine may have had a causal effect not only at the beginning of the process but also in its perpetuation and poor outcome. During the period of greatest risk (in this case, the first 3 months after starting clozapine),[3] our patient presented severe hypomotility that progressed to ischemic colitis with insufficient response to medical treatment. This generated an extremely poor general status and marked cachexia before the drug was withdrawn. The quick improvement after withdrawal (almost within 24 hours) with complete remission and no need for a new surgical intervention leads us to believe that clozapine had played an important role at the beginning and had also hindered the resolution of this complication by maintaining hypomotility and hypoperfusion.

Hence, we can conclude that, with timely withdrawal, even processes as advanced as the one we report can revert, thus preventing aggressive surgery and death. Clinical management should include attention to abdominal symptoms, early and suitable treatment of constipation, and, in the case of severe intestinal symptoms, withdrawal to prevent a fatal outcome.[15,16]

AUTHOR DISCLOSURE INFORMATION

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Treatment of Psychotic Depression in the Elderly Compared With Nonpsychotic Depression

To the Editors:

The are only a small number of treatment studies in elderly patients with psychotic depression. According to retrospective or open prospective studies, elderly patients with a psychotic depression respond poorly to treatment with medication, although electroconvulsive therapy (ECT) may be more effective.[1–4] We are aware of only 2 randomized, controlled trials (RCT) of acute treatment of elderly patients with a psychotic depression.[5,6] In the first trial, 36 patients were openly treated until a therapeutic plasma level of nortriptyline was reached and were then randomly assigned to addition-of-perphenazine or placebo group. No difference could be demonstrated between both groups.[5] In the second trial, 142 older patients were randomized to either olanzapine/sertraline or olanzapine/placebo, and the combination therapy showed superiority over placebo.[6]

We have recently finished a double-blind RCT in elderly inpatients with major depressive disorder, comparing venlafaxine with nortriptyline.[7] In that study, we found remission and response rates of 32.1% and 46.9%, respectively, with no significant difference between both treatments. The design of the study has been published in detail in our previous article.[7] In short, a double-blind, randomized 12-week parallel-group trial compared venlafaxine with nortriptyline in depressed inpatients, aged 60 years or older, with a unipolar major depression according to the *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria. In addition to the antidepressant, the patients could be openly treated during the RCT with haloperidol (maximum 5 mg/d), risperidone (maximum 2 mg/d), oxazepam (maximum 50 mg/d), or temazepam (maximum 20 mg/d). All patients were under similar nonpharmacological treatment regimen.

After the double-blind phase, the patients were asked to participate in an open follow-up study of 3 years' duration, in which antidepressant and other drug treatment was initiated at the psychiatrists' discretion. The primary efficacy outcome criterion was remission according to the Montgomery-Åsberg Depression Rating Scale (MADRS; final score, $\leq$10).[8] The Symptoms, Sign, Side Effect checklist was used to asses the presence and severity of 43 symptoms or adverse effects.[9] The primary safety outcome measure was the investigators' judgment at the end point of the overall clinical assessment of tolerance.[7]

The whole group consisted of 40 patients with a psychotic depression (16 receiving venlafaxine and 24, nortriptyline) and 41 patients with a nonpsychotic depression (24 receiving venlafaxine and 17, nortriptyline; $P = 0.095$). There were no differences in baseline demographic variables between both groups. Patients with a psychotic depression had a higher mean ± SD MADRS score (34.3 ± 6.7 vs 31.4 ± 5.4; $P = 0.034$) and a shorter duration of the present episode (3.9 ± 2.8 months vs 7.1 ± 5.1; $P < 0.001$) than patients with a nonpsychotic depression (Table 1). The mean scores on the Hamilton Depression Rating Scale, the Mini–Mental State Examination, the number of physical illnesses, and the number of somatic comedication did not differ significantly between both groups. In patients with psychotic features, the mean dosage of venlafaxine at the end point was 164 ± 88 mg/d and the mean final plasma level of venlafaxine and desmethylvenlafaxine was 603 ± 278 μg/L, whereas the mean dosage of nortriptyline was 96 ± 22 mg/d and the mean final plasma level was 113 ± 47 μg/L. This did not differ significantly from the plasma levels in patients without psychotic features.

At baseline, 27 patients already used an antipsychotic agent, and during the trial, 12 other patients started with an antipsychotic agent. The only psychotic patient who did not receive an antipsychotic agent had mild visual hallucinations at baseline, which disappeared during the trial. The mean maximum dosage of haloperidol equivalents during the trial was 2.2 ± 1.4 mg/d. Within a few weeks after successful treatment of psychotic features, the antipsychotic drugs were tapered down. Between patients with and without psychotic features, there were no statistically significant differences in dosages of other psychotropic medications or in the number of patients using them.

We could not demonstrate any statistically significant difference in efficacy or tolerability parameters between patients with and without psychotic features within the 12 weeks of double-blind treatment (Table 1). There were no significant changes in laboratory values and electrocardiograms in both treatment groups.

After the double-blind treatment phase, 26 patients with a psychotic depression had not achieved remission. Six patients achieved remission after continuing the antidepressant on which they already had achieved a significant improvement. Twenty other patients were treated with a switch to nortriptyline (remission, 2 of 6 patients), lithium augmentation (remission, 11 of 17 patients), phenelzine (remission, none of 7 patients), and ECT (remission, all 3 patients). With this strategy, 36 patients (90%) achieved remission and 39 (97.5%) achieved a

TABLE 1. Efficacy and Tolerability of Depressed Patients With and Without Psychotic Features (Intention-to-Treat Group)

	Psychotic	Nonpsychotic	*P*
Remission on MADRS (≤10), n (%)	14 (35)	12 (29.3)	0.580
Remission on HDRS (≤7), n (%)	12 (30)	10 (24.4)	0.570
Response on MADRS, n (%)	18 (45)	20 (48.8)	0.733
Response on HDRS, n (%)	20 (50)	16 (39.0)	0.320
CGI-I 1-2, n (%)	20 (50)	24 (58.5)	0.507
Mean (SD) reduction in MADRS	15.6 (14.8)	13.8 (10.9)	0.546
Mean (SD) reduction in HDRS	12.2 (10.1)	10.7 (7.5)	0.437
Mean (SD) time to achieve remission, wk	27 (28)	32 (44)	0.537
Mean (SD) No. adverse effects	4.7 (3.8)	6.1 (3.7)	0.11
Mean (SD) CAT	2.3 (0.9)	2.1 (0.6)	0.129
No. dropouts, (%)	15 (37.5%)	12 (29.3)	0.432

Response is defined as at least 50% reduction in score compared with baseline.

CAT indicates Clinical Assessment of Tolerability score; CGI-I, Clinical Global Impression of Improvement; HDRS Hamilton Depression Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale.

response within the 3 years of observation. Using the same treatment guideline, 32 (78.1%) of 41 patients with a nonpsychotic depression achieved remission; and 39 (95.1%), a response within the 3 years of observation (difference between psychotic and nonpsychotic patients, $P = 0.143$ and $P = 1.0$, respectively).

A Cox survival analysis with mean time to remission also showed no difference between patients with and without psychotic features (Wald, 0.215; *df*, 1; $P = 0.643$). Remission was predicted by a lower MADRS score at baseline (Wald, 6.093; *df*, 1; $P = 0.014$); psychotic features did not influence the chance of remission. The mean number of antidepressant treatments needed to achieve remission in psychotic patients (2.3 ± 1.1) was not different from that in nonpsychotic patients (2.5 ± 1.1; $P = 0.554$). The number of patients having a relapse or recurrence within the 3 years of observation (14 and 7, respectively; $P = 0.066$) also did not differ between patients with and without psychotic features.

In this study among elderly inpatients with a major depression, we could not demonstrate any statistically significant difference in efficacy or tolerability between psychotic versus nonpsychotic depression. Although replication in a larger sample size is needed, this study adds to the suggestion that psychotic depression in the elderly may not have a worse prognosis compared with nonpsychotic depression, at least on short term. Both trial medications were well tolerated in this inpatient group of elderly patients with significant physical comorbidity. Our remission rate in psychotic depressed patients of 35% is comparable with the results of both other RCTs in older patients with psychotic depression, if the slightly different outcome criteria are taken into account.[5,6] Another study in elderly patients with a psychotic depression found an impressive response rate of 76% after pharmacotherapy and ECT, but this was an open study.[3] Our study also demonstrates that after failure of an initial trial of an antidepressant combined with an antipsychotic agent, further treatment steps lead to an impressive remission rate of 90%, again with no differences between psychotic and nonpsychotic depressed elderly.

The most important limitations of our study were the small number of included patients and the open, nonrandomized treatment with antipsychotic agents. However, treatment was according to the Expert Consensus Guidelines on pharmacotherapy in older patients, which recommends either the combination of antidepressant and antipsychotic medication or ECT.[10]

AUTHOR DISCLOSURE INFORMATION

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Delirium Associated With Mianserin in Demented Patients

To the Editors:

Mianserin is a tetracyclic antidepressant with α2 antagonist properties.[1] Its use is recommended particularly in the elderly, as it is tolerated well compared with tricyclic antidepressants and selective serotonin reuptake inhibitors.[2] It has a recognized effectiveness against sleep disorders and is known to be used with more ease in the elderly, because of its having fewer drug interactions and being among the antidepressant drugs that minimally lower the epileptic threshold.[1,2]

Delirium is defined as the acute disturbance of consciousness and cognition over a short and fluctuating period.[3] Delirium has been reported to be superimposed on dementia in 22% to 89% of demented patients.[4–6] The patients exhibit perceptional disturbances, hallucinations, and agitations. Acute confusional states may occur more readily in the elderly than the young.[7] This readiness has been blamed on their heavier use of medications, as well as the changes in their brain neurochemistry associated with diseases of old age.[8] This article presents an acute confusional state associated with mianserin treatment, which was chosen on the assumption that it would have fewer adverse effects and be more reliable, administered for sleep disorders and depressive mood in 4 patients diagnosed with dementia.

CASE 1

An 83-year-old male patient had been followed up for 1.5 years for Alzheimer disease (AD)–type dementia. He also had a 10-year history of hypertension. The patient had moderate AD and had displayed recent delusions (that his wife was cheating on him) and unusual behavior (uncontrolled sexual behavior). He had been using 9 mg/d rivastigmine for the last 1½ years, 10 mg/d amlodipine for 10 years, 40 mg/d quinapril for 5 years, and 2.4 g/d piracetam for the last 1 year. He also received 10 mg/g olanzapine for his delusions in the last 6 months, which improved the symptoms markedly. Single-dose 30 mg/d mianserin was started in the evening for sleeping problems and depressive mood. A few hours after the administration of the drug, the patient became agitated and attacked the people around him. His spatial and personal orientation was disturbed. Routine blood and urine analyses conducted were found normal. A reexamination of his cardiac and respiratory systems did not reveal any new pathology. It was thought that the delirium manifestations of the patient might have arisen because of mianserin administration, and the drug was discontinued. The patient was restored to his normal condition the next day. A few days later, he was administered single-dose 15 mg/d mianserin in the evening for his insomnia complaints. The same acute confusional state appeared in the patient, who clinically recovered after the discontinuation of the drug.

CASE 2

A 70-year-old male patient had been followed for AD-type dementia for 4 years. The patient who had moderate AD-type dementia and delusions (he believed his house was robbed) had used 50 mg/d clozapine for 10 months. The patient also received 10 mg/d donepezil for 3 years and 20 mg/d memantine for the last 1½ years. For his insomnia and depressive mood, the patient was started on 30 mg/d mianserin. The patient experienced an acute disturbance of spatial and personal orientation and showed a marked state of dullness. His metabolic values were examined, but found normal. Possibility of an infection was excluded by analyses. There was also no cardiac or respiratory problem. Mianserin therapy was discontinued, and the patient resumed his previous state.

CASE 3

A 74-year-old male patient had been followed up for AD-type dementia for 3 years. The patient was on 10 mg/d donepezil for 2 years. The patient was started on 30 mg/d mianserin for his depressive mood and insomnia complaint. About 3 hours after receiving the drug, the patient became agitated and did not know where he was and who the people around him were. He gave nonsensical answers to questions directed to him. He recovered the next morning. His condition remained inexplicable. When his caretaker administered mianserin for his insomnia in the same evening, the same clinical manifestations appeared again, but vanished after discontinuation of mianserin.

CASE 4

A 67-year-old male patient had been followed up for 5 years for Parkinson dementia. The patient received 600 mg/d levodopa, 150 mg/d carbidopa, 800 mg/d entacapone (Stalevo 150 mg, 4 tablets per day) for 4 years, 10 mg/d donepezil for 2 years, and 100 mg/d quetiapine for 1 year. The patient was put on 30 mg/d mianserin for his depressive mood. The patient showed blurred consciousness, as well as disturbance of spatial, personal, and temporal orientation. He had an apathetic look and started talking nonsense. No pathology could be found to explain the deterioration in the clinical condition of the patient. Therefore, mianserin therapy was discontinued, and the patient recovered to his previous state.

DISCUSSION

Delirium is a common problem in demented patients.[4–6] As far as we know, there has been no report of delirium associated with the use of mianserin in demented patients in the literature. In the present article, we present delirium manifestations that appeared after the use of mianserin and vanished upon discontinuation of the drug in 4 demented patients. Mianserin is an antidepressant of the tetracyclic group and is the drug of choice in senior patients because of its weak anticholinergic property.[1] Interacting with presynaptic α2 autoreceptors of noradrenergic neurons, mianserin inhibits these receptors and leads to an increase in norepinephrine levels by lifting the inhibition of neurons.[1] It also acts on serotonergic neurons through α2 heteroreceptors and increases the amount of serotonin by eliminating the inhibitory effect of norepinephrine on serotonin release.[1]

Norepinephrine neurons in locus caeruleus innervate cell bodies of serotonergic neurons in the midbrain raphe.[1] This noradrenergic input elevates serotonin release via postsynaptic α1 receptor. As mianserin is also of an α1 antagonist character it enhances noradrenergic neurotransmission more than serotonergic neurotransmission.[1] Furthermore, it possesses 5-HT2A, 5-HT2C, 5-HT3, and H1 antagonist properties.[1] Blockage of 5-HT2 and 5-HT3 receptors may contribute to its anxiolytic and sleep-restoring effects. Besides, blockage of these 2 receptors

prevents the development of gastrointestinal symptoms (nausea, vomiting, diarrhea) and sexual dysfunction symptoms, which are considered adverse effects of selective serotonin reuptake inhibitor drugs.[2,9] Delirium is marked by modified consciousness, attention deficit, and fluctuating changes in cognitive functions. Its pathology has not been fully elucidated yet. However, it has been claimed that reduced cholinergic system function; elevated norepinephrine, dopamine, and glutamine secretion; impaired cerebral metabolism; and inflammatory response may be contributory factors.[3,7,8] If the manifestations of delirium do not include agitations, it may be overlooked by both clinicians and caretakers. Possibility of delirium should be carefully considered when there is a clinical deterioration in dementia patients, as seen in the cases presented in this study.

It is indicated in the literature that mianserin, which we administered to our patients, can be used in the treatment of delirium.[10] The literature also includes a few studies noting that mianserin leads to delirium in senior patients and those with organic brain syndrome.[11,12] However, we have not seen any article concerning the development of delirium in demented patients. We think that mianserin may cause this clinical situation by increasing noradrenergic transmission in locus caeruleus. One of our patients was simultaneously taking clozapine. Clozapine was reported to increase the norepinephrine levels in this area.[13] Thus, simultaneous use of these 2 drugs may increase the projections of norepinephrine neurons from locus caeruleus to other sites of brain such as forebrain. This may consequently result in an increase in the control of vigilance and initiation of adaptive responses that might have caused the delirium. At the same time, it has an antagonist effect against 5-HT3, which is found in the limbic system (hippocampus, amygdala) and cortical areas (piriform and entorhinal cortex).[2,9] This effect further adds to the increased norepinephrine response and may negatively affect attention. Mianserin is metabolized by CYP2D6 enzyme.[1] The drugs that our patients used were olanzapine and clozapine, and these drugs are basically metabolized by CYP1A2 enzyme, whereas minor concentrations have interactions with CYP2D6.[1] On the other hand, the majority of quetiapine was metabolized by CYP3A4 and by CYP2D6 in minor proportions.[1] The patients in our study had been using these antipsychotics for long periods; thus, this might have caused alterations in the enzyme systems. These alterations might alter the rate of metabolism of mianserin and other antipsychotics and increase the response to these drugs. Subsequently, delirium occurred in our patients. Delirium may manifest itself in patients using several drugs with central effects, when the above-listed factors are added to the neurotransmitter impairment caused by the disease in the brain.

In conclusion, acute changes in attention, cognition, and behavior should be carefully observed and should be taken into consideration as a possible manifestation of delirium.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Serotonin Syndrome With Sertraline and Indomethacin

To the Editors:

Serotonin syndrome (SS) is a potentially life-threatening adverse drug reaction manifesting in mental status changes and autonomic and neuromuscular hyperactivity. Serotonin syndrome is caused by an increased serotonergic activity in the central and peripheral nervous system. Serotonin modulates attention, behavior, and thermoregulation in the central nervous system. In the peripheral nervous system, serotonin is involved in regulating vasoconstriction, bronchoconstriction, gastrointestinal motility, and uterine contraction.[1]

Serotonin syndrome is a clinical diagnosis in accordance with the Hunter Toxicity Criteria decision rules.[2] To fulfill the Hunter Toxicity Criteria, the patient must have taken a serotonergic agent and must have one of the following symptoms: (1) spontaneous clonus, (2) inducible clonus plus agitation, (3) ocular clonus plus agitation or diaphoresis, (4) tremor and hyperreflexia, and (5) hypertonia and a temperature higher than 38°C plus ocular clonus or inducible clonus. No laboratory test can confirm the diagnosis. The serum serotonin concentration does not correlate with the severity of SS.

A 43-year-old woman was admitted to our emergency department in coma. Her partner said she felt uncomfortable and complained of headache, could not stop shivering, and vomited before she lost consciousness. Because he thought she had a cardiac arrest, he started cardiopulmonary resuscitation. The patient had a history of depression and had been treated with sertraline 100 mg once daily for 2 years. Three days before presentation, she started treatment with indomethacin 75 mg 2 times daily because of

shoulder pain. She did not take any other medication or drugs. She was a smoker for 20 years, and her mother had had a myocardial infarction at a young age. At presentation, her blood pressure was 150/100 mm Hg; heart rate, 125 beats per minute; and core temperature, 36.5°C. She had a flushed skin, sweated excessively, and had diarrhea. Neurological examination demonstrated a comatose patient (Glasgow Coma Scale score, E1M2V1), with intermittent tremor, mydriasis, normal pupillary light reflexes, normal corneal reflexes, and oculocephalic reflex. Her extremities showed extreme rigidity, with lower extremity hyperreflexia, inducible ankle clonus, and Babinski signs. Laboratory studies were significant for elevated aspartate aminotransferase (220 IU/L), alanine aminotransferase (275 U/L), and lactate dehydrogenase (553 IU/L) levels and leukocyte count (13.3×10^9/L). The creatine kinase level was normal (94 U/L), and the troponin level was slightly elevated (0.13 μg/L), probably because of cardiopulmonary resuscitation. Arterial blood gas analysis revealed a metabolic acidosis (pH 7.19; P_{CO_2}, 5.2; HCO_3, 15; Base excess, 12.9; P_{O_2}, 30.7) with an increased anion gap. Toxicologic blood screening showed therapeutic levels of sertraline 0.026 mg/L (0.025–0.10 mg/L), desmethylsertraline 0.045 mg/L (0.050–0.20 mg/L), and indomethacin 0.16 mg/L (0.08–0.25 mg/L). Urine toxicologic examination was not performed. Electrocardiography and cerebral computed tomography had normal results. Lumbar puncture showed a normal pressure, no white blood cells, glucose level 5.05 mmol/L (serum glucose level, 17 mmol/L), and protein level 0.60 g/L (0.27–0.60 g/L). The cerebrospinal fluid culture was negative for any microorganisms. The patient was intubated and transferred to the intensive care unit. Intravenous midazolam was given for sedation and to restrict rhabdomyolysis. The serotonergic antagonist cyproheptadine was started. Within 12 hours, she was extubated but still confused. Within 4 days, she was discharged from hospital with a normal mental status but with amnesia for her admission and intensive care period. After discharge, she did not use sertraline, indomethacin, or any other nonsteroidal anti-inflammatory drug. Within 25 days, she was readmitted because of chest pain for 2 days and had a diagnosis of myocardial infarction (Electrocardiography showed sinus rhythm of 80/min, with q wave in leads II, III, and aVF; negative T waves in leads I, II, aVL, and aVF; and very deep negative T waves in lead V_2 t/m V_6 with a serum troponin I level of 1.15 μg/L and a creatine kinase level of 68 U/L.). During cardiac catheterization, a stent was placed in the left anterior descending artery because of an atherosclerotic plaque and vasospasm.

We describe a young patient with clear SS; she had taken a serotonergic agent and had 4 of 5 symptoms of the Hunter Toxicity Criteria. Serotonin syndrome is an important drug-related complication in people who use psychopharmacologic therapy and has been described previously in patients using sertraline. Our patient used sertraline for more than 2 years without adverse effects. Theoretically, she could have taken an overdose, but sertraline and desmethylsertraline levels in her blood were in a therapeutic level. However, she started indomethacin treatment 3 days before occurrence of the SS. Indomethacin has no known serotonergic effect but is a potent inhibitor of the CYP 2C9 protein, whereas sertraline is partly metabolized and converted to *O*-desmethylsertraline through this enzyme.[3–5] However, 6 different isoforms of CYP (CYP 3A, CYP 2C9, CYP 2E1, CYP 2C19, CYP 2D6, and CYP 2B6) are involved in sertraline *N*-demethylation.[6–8] Therefore, concurrent administration of a drug that inhibits 1 specific CYP isoform is unlikely to cause a marked increase in the plasma concentration of sertraline, as is demonstrated in our patient. By polymerase chain reaction, we tested the CYP 2C9 genotype for the 2 most frequent CYP 2C9 variant alleles that have less enzyme activity: R144C (*2) and 1359L (*3).[9] However, our patient seemed to be a normal metabolizer. In addition, the metabolite desmethylsertraline is not relevant in this clinical event because it has very little pharmacologic activity.[10] In summary, we have no pharmacokinetic explanation for the observed effects. Both indomethacin and serotonin are indole derivatives. Approximately half of the dose is *O*-demethylated, and a portion is also *N*-deacylated.[11] The remaining metabolite shows a striking structural similarity with serotonin. Indomethacin is also known for its central nervous system toxicity, and we hypothesize that this metabolite may have either acted as a serotonin reuptake inhibitor or a serotonin agonist in our patient.

Our patient recovered entirely from the SS, but during her second admission, she had myocardial infarction. To our knowledge, there is only 1 other case described where a young woman with SS developed acute myocardial infarction, occurring at the same time.[12] Golino et al[13] described how serotonin has divergent effects on coronary arteries; it dilates normal coronary arteries and constricts diseased ones. There are many studies that investigated the association of selective serotonin reuptake inhibitors and acute myocardial infarction with opposite results.[14] Our patient had cardiovascular risk factors and must have had coronary artery disease previously, so excess serotonin or its metabolites may have triggered the coronary spasm. However, the long delay of more than 3 weeks after SS makes a causal relation speculative.

This patient history is of clinical importance because it shows an interaction between sertraline and indomethacin, which has not been described before, leading to a dramatic clinical picture of SS. Moreover, it strengthens a previously described relation of SS with myocardial infarction.

AUTHOR DISCLOSURE INFORMATION

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Ziprasidone, Monoamine Oxidase Inhibitors, and the Serotonin Syndrome

To the Editors:

Augmenting antidepressants with second-generation antipsychotics (SGAs) is a strategy with increasing clinical and research evidence supporting its use.[1,2] Because both SGAs and many antidepressants (especially selective serotonin reuptake inhibitors [SSRIs], dual action agents, and monoamine oxidase [MAO] inhibitors) enhance serotonergic function, excessive serotonergic tone may theoretically result from the combination of an SGA with any of these medication classes.[3,4] Increased serotonergic activity in the central nervous system can lead to serotonin syndrome, characterized by a triad of mental status changes, autonomic instability, and neuromuscular excitation caused by excessive stimulation of 5-HT2A receptors.[5–9] In the following case, low-dose ziprasidone and therapeutically dosed tranylcypromine precipitated a serotonin syndrome.

Mrs B. is a 41-year-old woman referred for treatment of severe treatment-refractory chronic major depression with atypical features. Her most recent medication regimen, which resulted in less than 25% improvement, included bupropion XL 450 mg daily, duloxetine 120 mg daily, and ziprasidone 40 mg. In lieu of electroconvulsive therapy, a MAO inhibitor trial was recommended. The patient was given instructions to gradually reduce and after 2 weeks eliminate duloxetine and bupropion. Ziprasidone was continued because it helped in the patient's anxiety, and she felt more comfortable continuing 1 medication that could help her during the cross-titration process. MEDLINE review of the literature did not report any adverse drug reactions between MAO inhibitors and SGAs. After a 14-day washout from bupropion and duloxetine, Mrs B. started tranylcypromine at 10 mg daily. During this titration process, she denied any changes in mental status and muscle tone and exhibited stable vital signs but did report intermittent diarrhea, dizziness, and insomnia. On day 23 of tranylcypromine treatment, the dose was increased to 50 mg/d in divided doses. By the next day, the patient reported acute onset of shivering, tremors, profuse diaphoresis, fever, vomiting, diarrhea, and increased confusion. Her husband took her to the emergency room when she was unresponsive but writhing on the ground with myoclonic jerks of the lower extremities. In the emergency department, the patient was agitated, disoriented, febrile to 38.5°C, with pulse rate of 130 beats/min and blood pressure of 180/100 mm Hg. She was shivering, hyperreflexic, and exhibiting myoclonic jerks of all 4 extremities requiring restraints. Conservative cooling measures, intravenous fluids, and intravenous lorazepam 12 mg in 2 doses rapidly improved symptoms of altered mental status, autonomic instability, and neuromuscular excitation. There was no evidence of infection as evidenced by negative urine cultures, blood cultures, and chest radiographs. In addition, there was no ingestion of a surreptitious agent as cough syrup or any pain medication, no consumption of fermented foods, and no changes in the ziprasidone dose. A urine toxicology screen was negative. She was admitted to the intensive care unit where she did not require further pharmacological management. Most of Mrs B.'s symptoms resolved within 24 hours, and after 2 days, when the patient was essentially asymptomatic, she was discharged from hospital.

The patient's presentation is consistent with significant serotonin toxicity based on the Hunter Serotonin Toxicity Criteria.[7,9] In the emergency department, she exhibited spontaneous clonus, myoclonus, hyperreflexia, diaphoresis, and pyrexia (>38°C), suggesting severe serotonin toxicity. Serotonin toxicity was distinguished from neuroleptic malignant syndrome by the absence of extrapyramidal features, lead-pipe rigidity, and bradykinesia. In addition, the presence of neuromuscular excitation and lack of exposure to other agents ruled out encephalopathy, anticholinergic delirium, sympathomimetic toxicity, and malignant hyperthermia. After beginning conservative cooling measures, sedation, and supportive care, Mrs B.'s symptoms resolved, mostly within 12 to 24 hours.

The Hunter Area Toxicology Service (HATS) data from more than 2000 serotonergic overdoses formulate serotonin toxicity as a spectrum concept ranging from serotonin adverse effects to severe life-threatening toxicity.[7,9] A drug's potency to increase intrasynaptic serotonin coincides with the degree of serotonin toxicity mostly by excessive activation of 5-HT2a receptors.[8,9] Serotonin toxicity is associated with drugs increasing serotonin by 3 mechanisms of action: inhibition of reuptake, presynaptic release, and MAO inhibition. However, at high concentrations, serotonin could displace an inhibitor from the enzyme or reuptake inhibitor, thereby limiting the degree of serotonin toxicity and suggesting a ceiling effect.[8–10] The HATS database estimates 15% of SSRI-alone overdoses lead to moderate serotonin toxicity with no pyrexia (>39°C), and high concentrations of a reversible MAO-A inhibitor alone are not associated with severe serotonin toxicity.[8,9,11] On the other hand, HATS data indicate that 25% of overdoses involving moclobemide and SSRIs lead to the most severe cases of serotonin toxicity.[12,13] In addition, there are numerous reports of MAO inhibitors independently and in combination with another serotonergic agent causing serotonin toxicity.[14–16]

The proposed mechanism of serotonin toxicity in this patient is enhanced serotonin via inhibition of metabolism by tranylcypromine and the multiple serotonergic effects of ziprasidone. These include direct stimulation of 5-HT1a receptors;

antagonism of 5-HT1d presynaptic autoreceptors, which normally inhibit serotonin release and when blocked enhance serotonergic function; 5-HT1a agonist activity similar to buspirone; antagonism of 5-HT2a and 5-HT2c receptors; and inhibition of serotonin reuptake.[17,18] Of these, the inhibition of serotonin reuptake may be the most important in predicting risk of serotonin syndrome when prescribed in conjunction with a MAO inhibitor. Among all the current SGAs, ziprasidone exhibits the highest 5-HT2a/D2, 5-HT2c/D2, and 5-HT1a/D2 receptor-binding ratios[17,18] and may therefore be the most likely to demonstrate an interaction with MAO inhibitors.

After discharge from the hospital and 1 week after discontinuing ziprasidone, the patient restarted tranylcypromine 10 mg daily and increased the dose by 10 mg every week. She required fludrocortisone 0.1 mg daily and a high-salt diet to offset orthostatic adverse effects. Throughout her treatment, the patient also took lorazepam 1 mg for sleep. Mrs B. reached a target dose of 80 mg/d of tranylcypromine with no signs of serotonergic toxicity. After 2 months on tranylcypromine 80 mg/d and then augmented with methylphenidate 20 mg twice a day, the patient reported a 50% improvement in symptoms.

This is the first case report of serotonin syndrome between a MAO inhibitor, tranylcypromine, and ziprasidone. The possibility of spontaneous serotonin syndrome from tranylcypromine alone is unlikely because Mrs B. was able to tolerate higher doses of tranylcypromine (up to 80 mg/d) in the absence of ziprasidone. Given the increasing use of SGAs in treatment-refractory depression, clinicians should consider the possibility of serotonin syndrome if the primary antidepressant is a MAO inhibitor.

AUTHOR DISCLOSURE INFORMATION

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Primary Add-on of Ziprasidone in Sertraline Treatment of Posttraumatic Stress Disorder
Lessons From a Stopped Trial?

To the Editors:

Selective serotonin reuptake inhibitors (SSRIs), such as sertraline and paroxetine, are currently the approved medication of choice for posttraumatic stress disorder (PTSD).[1] However, it takes several weeks before they ameliorate symptoms, and there is a considerable rate of nonremission. Therefore, it is a tempting strategy to add additional drugs, either during the first weeks of SSRI treatment to potentially accelerate symptomatic relief (primary add-on) or after unsatisfactory response after several weeks of SSRI treatment (classic augmentation).

Alongside other atypical neuroleptics,[2] ziprasidone has been proposed as a promising adjunctive agent in the treatment of anxiety-spectrum disorders and depression after an insufficient response to SSRI.[3,4] In addition to dopamine-2 and 5-HT_{2A} (serotonin type 2A) receptor antagonism, ziprasidone is a potent 5-HT_{1A} receptor agonist and also inhibits reuptake of 5-HT and norepinephrine with potency comparable with that of imipramine. Impressive acute anxiolytic effects of ziprasidone have been shown in subjects before dental surgery.[5]

However, until now, only few casuistic reports have been published about ziprasidone therapy in PTSD patients. Frecska et al[6] reported successful monotherapy with 80 mg 2 times a day (bid) in a previously treatment refractory patient with PTSD. Symptoms recurred after discontinuation, but after reinstallment of ziprasidone therapy, remission was achieved again. Siddiqui et al[7] reported 2 cases of PTSD patients who had not responded to various psychopharmacotherapy but decidedly ameliorated under ziprasidone.

One subject received 80 mg bid in monotherapy, another 60 mg bid (together with trazodone and topiramate). Studies in PTSD using ziprasidone for augmentation are still missing.

Against this background, we designed a pilot study about the effects of primary add-on of ziprasidone to standard SSRI treatment in PTSD patients.

In a double-blind, equally randomized, placebo-controlled design, we intended to administer ziprasidone as an add-on during the first 4 weeks of sertraline treatment in 24 adult patients with chronic PTSD (according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*). Patients with lifetime psychotic disorders, current substance dependence, gravidity, lactation, tartrazine hypersensitivity, and contraindications against sertraline or ziprasidone were excluded. The protocol was approved by the ethics committee of the Medical Board Hamburg. Patients gave written informed consent before participation. The protocol was registered in the Clinical Trials.gov Identifier under NCT00248261.

Daily doses of ziprasidone (Zeldox; Pfizer GmbH, Karlsruhe, Germany) were 40 mg on days 1 and 2, 80 mg on days 3 and 4, 120 mg on days 5 and 6, and 160 mg on days 7 to 28. In case of adverse effects, dosage reduction after day 8 to a minimum of 80 mg/d was permitted.

A standard sertraline (Zoloft; Pfizer GmbH, Karlsruhe, Germany) therapy was begun in all subjects with 25 mg/d during week 1 and increased by 25 mg every week until 100 mg/d; for weeks 4 to 8, a fixed dosage of 100 mg/d was to be given.

Primary outcome parameters were the ratings on the Post-traumatic Diagnostic Scale and Beck Depression Inventory, which were to be filled in on days 0, 14, 28, 42, and 56. We hypothesized significantly lower Post-traumatic Diagnostic Scale and Beck Depression Inventory ratings at days 14 and 28 in the ziprasidone versus placebo group.

Three of the first 7 patients terminated study participation because of intolerable adverse effects before the day 14 ratings (specifically on days 6, 7, and 9). They had nausea, headache, trembling, and palpitations (woman, 29 years); dizziness, vertigo, and impaired vision (man, 51 years) and rigidity in the jaws, diarrhea, fatigue, vertigo, and impeded micturition (woman, 35 years).

We decided to deblind the codes of these first 7 subjects to check for ethical feasibility to continue this study. We found out that all 3 early dropouts had received ziprasidone add-on (with dosages of 120–160 mg/d), whereas the other 4 subjects, who stayed in the trial without major adverse effects, had received a placebo add-on.

Applying the χ^2 test on a respective 2×2 table (frequency distribution: placebo dropout, 0; placebo nondropout, 4; ziprasidone dropout, 3; and ziprasidone nondropout, 0) yields $\chi^2_1 = 7.0$ ($P < 0.01$). Thus, the frequency distribution of dropouts in the ziprasidone group is significantly higher than in the placebo group. We considered this finding sufficient reason to decide to terminate this trial.

DISCUSSION

Notwithstanding our results, further studies about the potential therapeutic use and safety of ziprasidone in PTSD patients treated with SSRI are clearly warranted. However, lower initial doses of ziprasidone and a slower dose increase, maybe as well a reduced final dose, might be advisable.

Our initial protocol was inspired by a recent study on adjunctive ziprasidone in treatment-resistant depressed patients under sertraline therapy.[4] After brief dosage titration, subjects in this study were assigned to 160 mg/d already on day 5, and despite a considerable rate of adverse events, no dropouts were observed. However, it cannot be excluded that anxiety disorder patients, such as subjects with PTSD, may be more prone to experience adverse effects of ziprasidone in comparison with depressed or schizophrenic patients. Crane[3] reported successful augmentation with ziprasidone in cases of patients with panic disorder and obsessive compulsive disorder, who failed to respond to SSRI. They started with 20 mg/d, and doses were increased by 20 mg at weekly intervals. The authors found effective dosages of ziprasidone in these anxiety-spectrum disorders to be approximately only 40 to 80 mg/d and hence much lower than in schizophrenic patients (who would usually receive 160–320 mg/d). However, in the 2 case reports about ziprasidone treatment in PTSD mentioned earlier, 120 to 160 mg/d were well tolerated: Siddiqui et al[7] described successful titration over the course of only 1 week, whereas Frecska et al[6] did not report the speed of titration.

The adverse effects reported in our study cannot be clearly ascribed to ziprasidone alone but could also be due to increased serotonergic adverse effects of sertraline along with ziprasidone. Although interactions via cytochrome p450 can be excluded as a potential explanation,[8] overstimulation of 5-HT_{1A} receptors in central gray nuclei and the medulla via a combination of 5-HT reuptake inhibition by both drugs and considerable specific 5-HT_{1A} agonist activity of ziprasidone must be taken into account.[9] However, a pilot study on 5-HT_{1A} receptor binding in patients with PTSD has not shown altered expression using positron emission tomography,[10] which could have contributed to explain our finding. Thus, further studies are needed to clarify the biological underpinnings of our results and the role of ziprasidone in the treatment of PTSD.

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AUTHOR DISCLOSURE INFORMATION

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Clinically Relevant Pharmacokinetic Interaction Between Venlafaxine and Bupropion
A Case Series

To the Editors:

Venlafaxine is one of the most frequently prescribed antidepressants that acts as a serotonin and norepinephrine reuptake inhibitor. It is a known substrate for CYP450 2D6, which converts it to the active metabolite, desvenlafaxine.[1] After venlafaxine administration, the plasma levels of venlafaxine are normally about half of those for desvenlafaxine, which is not a substrate for CYP450 enzymes, including 2D6. Variability in plasma levels of venlafaxine versus desvenlafaxine can be due to genetic polymorphisms for CYP450 2D6. The concomitant administration of a drug that is a CYP450 2D6 inhibitor will also shift drug plasma levels toward more venlafaxine and less desvenlafaxine and will therefore not only reduce the relative amount of desvenlafaxine-induced NET inhibition, but also cause more adverse effects.[2] Several antidepressants have been described as CYP450 2D6 inhibitors.

In the case of treatment-resistant patients, combination strategies with the norepinephrine and dopamine reuptake inhibitor, bupropion, have been rather encouraged so far in the literature, even in large-scale studies such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (eg, see DeBattista[3] and Trivedi et al[4]). The combination of venlafaxine and bupropion has been referred to as a "heroic combo," because it leads to a multiple boost in neurotransmitter-induced actions.[5]

Here we present exemplarily the cases of 3 patients with a major depressive episode treated with venlafaxine and—because of insufficient treatment response—additionally with bupropion and the effects of this combination on serum levels of venlafaxine.

CASE

All 3 patients presented here had major depressive disorder and stated typical melancholic features, including depressed mood, anhedonia, lack of impetus, sleep and appetite loss, and symptom aggravation especially in the morning hours.

A 38-year-old woman was being treated for a recurrent depressive episode with 300 mg venlafaxine, 450 mg lithium, and 300 mg pregabalin per day at the time of admission to our hospital. As plasma drug levels of venlafaxine and desvenlafaxine were within the normal therapeutic range, we considered this patient to be a "normal metabolizer" and raised the daily venlafaxine dose to 375 mg to boost treatment response. Under this dosage, the steady-state plasma drug levels for venlafaxine amounted to 156 μg/L (suggested therapeutic range, 30–175 μg/L), and for desvenlafaxine, 392 μg/L (60–325 μg/L). Because of inadequate response to treatment in overall symptoms, we then decided to add bupropion as a dopaminergic boost to the treatment regimen. The combination of venlafaxine and 300 mg bupropion, however, caused a dramatic increase in levels of venlafaxine (864 μg/L) and desvenlafaxine (559 μg/L). The patient reported severe serotonergic adverse effects including tension, agitation, headache, and insomnia. Medication with bupropion was stopped, and venlafaxine was reduced to 225 mg. This resulted in a decline in serum venlafaxine levels (220 μg/L), with desvenlafaxine levels still being slightly elevated (443 μg/L) a week after cessation of bupropion. The reported adverse effects withered.

A 55-year-old woman was admitted to our hospital for treatment of her first severe depressive episode. At the time of admission, the patient was being treated with 225 mg venlafaxine, 30 mg mirtazapine, and 200 mg opipramol per day. Blood levels for venlafaxine (251 μg/L) and for desvenlafaxine (628 μg/L) exceeded those of the recommended therapeutic range. The patient was characterized as a "poor metabolizer," and the venlafaxine dose was reduced to 150 mg/d. Again, we decided to add bupropion to enhance clinical amelioration. The combination with 300 mg bupropion resulted in a further increase in serum levels of venlafaxine (308 μg/L) and a decrease in levels of desvenlafaxine (66.9 μg/L). The patient noticed a surge in inner tension. A further reduction of venlafaxine to 75 mg/d resulted in normal drug serum levels for venlafaxine (107 μg/L) but low levels for desvenlafaxine (21.6 μg/L). The medication with bupropion was carried on, as it substantially contributed to the patient's remission. Similar clinical courses and a relevant interaction between bupropion and venlafaxine were documented in at least 2 more cases.

A 47-year-old woman was being treated with 375 mg venlafaxine per day at the time of hospital admission. This patient was categorized as a rather "extensive metabolizer" after drug monitoring had revealed low venlafaxine levels (38.9 μg/L) and high desvenlafaxine levels (204 μg/L). Lacking sufficient treatment response, we used bupropion as a dopaminergic add-on. Only 150 mg bupropion was necessary in this patient to raise venlafaxine levels to 88.6 μg/L and desvenlafaxine levels to 222 μg/L. The combination of venlafaxine and bupropion redounded to remission of symptoms. In this case, the drug combination was well tolerated.

DISCUSSION

Although the addition of bupropion turned out to be in favor of recovery in 2 of 3 cases, a significant dose reduction of venlafaxine was necessary to avoid serotonergic adverse effects due to a clinically relevant inhibition of CYP450 2D6 by bupropion, leading to raised blood levels for venlafaxine. One patient stated mild adverse effects and 1 patient presented with severe serotonergic adverse effects.

In general, combination treatment can play an important role in remission from major depression, with bupropion being the most popular add-on strategy in a survey of more than 400 psychiatrists some years ago,[6] despite the fact that nearly all data supporting such a use came from case-series reports and small open trials.[3,7] Later, further studies—including the STAR*D trial—described a good overall tolerability and efficacy of bupropion add-on to selective serotonin reuptake inhibitors, thus supporting its use.[4,8–10] However, although in the above studies adverse effects were quite common and interactions with CYP450 isoenzymes were partly discussed, specific effects of antidepressants on mutual blood drug concentrations were not mentioned.

Although bupropion was initially thought to be a weak inhibitor of CYP2D6 in vitro,[11] subsequent in vivo studies demonstrated that this antidepressant may inhibit CYP2D6 activity in a clinically relevant manner and even cause tricyclic antidepressant toxicity.[12–17] An open-label pharmacokinetic study of bupropion added to venlafaxine or selective serotonin reuptake inhibitors in depressed patients found that bupropion was associated with a 2.5-fold increase in steady-state concentrations of venlafaxine.[14] However, the elevation of venlafaxine levels was not considered as clinically relevant by the authors.

According to our observations, the pharmacokinetic interaction of venlafaxine and bupropion should be taken into account, and the combination of the 2 drugs should be accompanied by therapeutic drug monitoring, and risk-benefit assessment, especially in "poor metabolizers" for 2D6.

AUTHOR DISCLOSURE INFORMATION

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Aripiprazole-Related Subcortical Growth in a Patient With Major Depressive Disorder and Panic Disorder

To the Editors:

Aripiprazole's D_2 partial agonist, serotonin 1A ($5\text{-}HT_{1A}$) partial agonist, and $5\text{-}HT_{2C}$ antagonist theory contributes to its add-on therapy role to major depressive disorder (MDD).[1] Its role in human subcortical structures is still unclear. Here, I want to present a case of MDD with panic disorder (PD) responding to aripiprazole treatment. His hippocampus, caudate, and putamen volume increased after a 6-week therapy.

CASE REPORT

Our patient is a 42-year-old man with single MDD with PD episode for 2 years (Hamilton Rating Scale for Depression [HAM-D], 41; Panic Disorder Severity Scale [PDSS], 25). He received the following antidepressants: fluoxetine, paroxetine, and venlafaxine, each for 3 to 4 months without much improvement (HAM-D lowest score, 39; PDSS lowest score, 22). Intolerable adverse effects, such as nausea, vomiting, occasional irritability, fatigue, and body weight gain, were mentioned while receiving these antidepressants. Irregular medicine adherence was noted and probably related to these adverse effects. No specific physical illness, psychotic features, past manic episodes, nonpsychiatric medication use, and substance abuse was mentioned. Because of treatment nonresponse and intolerable adverse effects, he started receiving aripiprazole 5 mg initially with abrupt switching from venlafaxine 150 mg/d (HAM-D, 41; PDSS,

TABLE 1. Subcortical Volume Increase After a 6-Week Therapy of Aripiprazole

Volume Area	Baseline Volume (mm^3)	6-wk Volume (mm^3)
Right hippocampus	4557.942383	4804.454590
Left hippocampus	4905.682617	5185.056641
Left caudate	4650.772461	5189.182617
Right putamen	4684.810059	5074.692383

25) and titrated to 10 mg within 2 weeks without any significant adverse effects except mild akathisia. After a 6-week therapy, his MDD and PD symptoms improved (HAM-D, 21; PDSS, 10).

The patient gave informed consent.

Structural brain magnetic resonance imaging (MRI) scans were obtained with 3-T GE version scanner housed at Buddhist Tzu Chi Hospital, Taipei. Scans with 3-dimensional fast-spoiled gradient-echo recovery T1-weighted images (TR = 11.2 milliseconds, TE = 5.2 milliseconds, matrix = 256 × 256, field of view = 260 mm, number of excitation = 1, slice thickness = 1 mm, 180 slices, and no gap) were performed on the first visit and on the sixth week of visit. His body weight remained similar, and no significant change of hydration status was observed in these 6 weeks (76.2–76.5 kg). Structural MRI was preprocessing with FMRIB's Integrated Registration and Segmentation Tool function (FIRST version 1.2) of FSL (version 4.1.1; FMRIB Software Library, Oxford University, London, England) to perform subcortical brain segmentation using shape and appearance model. Bilateral hippocampus, left caudate, and right putamen volume increased more than 200 mm^3 after a 6-week therapy of aripiprazole (Table 1).

DISCUSSION

Hippocampus is an important structure for mood and memory. Fear memory stored in the hippocampus would provoke panic attacks, and fear extinction would provide advantage to relieve panic attacks. Neuroimaging studies also suggested that the hippocampal volume was important for mood regulation.[2] The hippocampus has been reported to shrink in MDD and PD.[3,4] In this case, hippocampal growth was accompanied with clinical symptom improvement within 6 weeks. Aripiprazole has been reported to modulate rat hippocampus by increasing 5-HT_{1A} receptor binding sensitivity over the CA1 region.[5] A dopamine-enhanced release over the hippocampus was observed while rats were administered with aripiprazole at lower dose.[6] It is suggested that aripiprazole's D_2 partial agonist and 5-HT_{1A} partial agonist effect might play a role in hippocampus plasticity. Besides neurotransmitter theory, oxidative stress theory might also explain this hippocampus growth phenomenon. Martins et al[7] found that olanzapine and aripiprazole would not produce oxidative damage over the hippocampus and that their modulation of oxidative stress might provide their neuroplasticity. These findings might correspond to my findings that human brain MRI of 5-HT_{2C} antagonism can relieve the anxiety associated with depression and also facilitate neurogenesis,[8] which might also suggest the 5-HT_{2C} antagonist role of aripiprazole in the treatment of MDD with PD.

The caudate and putamen are usually related to motor function. Sheline[9] proposed a theory of limbic-cortical-striatal-pallidal-thalamic circuit in MDD pathogenesis. From a positron emission tomography study, aripiprazole would occupy D_2 receptors with a high percentage at the caudate and putamen (both >80%) in patients with schizophrenia without any extrapyramidal effects.[10] D_2 receptor occupancy is higher than that of 5-HT_{2A} receptors. Grunder et al[11] also found that D_2 occupancy was very high but without extrapyramidal adverse effects. They postulated that weak antagonism of D_2 might contribute to this finding. From these articles, caudate and putamen growth might be related to aripiprazole's high occupancy and D_2 partial agonist's effects.

From these results and discussion, a possible role of D_2, 5-HT_{1A} partial agonist, and 5-HT_{2C} antagonist could explain the "subcortical growth" of aripiprazole in this patient with MDD and PD.

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Reduced Cannabis Use After Low-Dose Naltrexone Addition to Opioid Detoxification

To the Editors:

Although the influence of cannabis use on the abuse of other drugs or their treatment may vary,[1,2] the increasing severity of cannabis use and its resistance to treatment warrant looking for more effective intervention strategies.[3] Multiple interactions exist between opioid and cannabinoid systems; opioid antagonist medications such as naltrexone (NTX) at low doses have been proposed to reduce cannabis reinforcement and consumption.[4] In a randomized, double-blind, placebo-controlled clinical trial, we found that daily addition to methadone taper of very-low-dose NTX (VLNTX, 0.125 mg/d, 0.250 mg/d) was associated with attenuated opioid withdrawal during inpatient detoxification and with reduced use of opioids and cannabis, measured by urine drug testing and self-report the day after discharge (D1) and 1 week later (D7).[5] The study was carried out in accordance with the Declaration of Helsinki and was approved by the institutional review boards of Duke University, Durham, NC, and Thomas Jefferson University, Philadelphia, Pa.

We examined follow-up data to explore factors associated with cannabis use after detoxification, in addition to VLNTX treatment, and determine whether such use affected short-term outcomes after discharge.

It is difficult to identify new cannabis use with urine testing at weekly intervals, because of the long excretion half-life in urine of cannabinoid metabolites.[6] As self-reported use of other drugs was reliably associated with urine test results in this sample (Fisher exact test: opioids, $P = 0.01$; cocaine, $P = 0.001$), self-reports were utilized as the primary data source for cannabis use at follow-up. Of 120 subjects completing detoxification, 96 were evaluated on D1, 48 of whom were using cannabis at study entry. Among the 61 evaluated on D7, 27 were positive for cannabis at admission. There was no significant difference in proportion of cannabis users randomized to VLNTX or placebo treatment groups (NTX 0.125 mg = 26.9%, NTX 0.25 mg = 35.9%, placebo = 37.2%). There were no significant differences in demographic or clinical characteristics between subjects lost to follow-up and those who participated in the evaluation (data not shown). There were no significant differences at admission between cannabis users receiving different treatments and between users and nonusers who participated in follow-up evaluations in terms of demographic, other drug use, and clinical characteristics, or proportion of subjects lost to follow-up (data not shown), except that cannabis users reported less frequent alcohol use ($\chi^2_2 = 7.0$, $P = 0.03$).

Cannabis use was detected in 22.9% of all patients on D1 and 34.5% on D7. Cannabis use on D1 was significantly associated with cannabis use at admission (Fisher exact test, $P = 0.03$), with cannabis use by D7 (Fisher exact test, $P = 0.001$), and with opioid use on D1 (Fisher exact test, $P = 0.001$) and D7 (Fisher exact test, $P = 0.001$). Cannabis use was not significantly associated with alcohol or any other drug use (data not shown). Cannabis use on D1 was also significantly associated with opioid withdrawal and craving intensity, measured by the Subjective and Objective Opioid Withdrawal Scales,[7] after adjusting for admission ratings by analysis of covariance: subjective ($F_{1,94} = 20.4$, $P = 0.001$), objective ($F_{1,93} = 16.4$, $P = 0.001$), and craving ($F_{1,89} = 9.9$, $P = 0.002$).

Very-low-dose NTX addition to detoxification was associated with significantly less cannabis use, both on D1 ($\chi^2_2 = 42.3$, $P = 0.001$) and D7 ($\chi^2_2 = 28.4$, $P = 0.001$). Fifty-one percent of subjects receiving placebo used cannabis within 24 hours after treatment completion versus 12% of the VLNTX-treated patients.

At D7, 41% (25/61) of subjects were attending drug-free structured outpatient programs. Fifty-six percent (14/25) of subjects in treatment were using drugs; no polysubstance use was detected. Cannabis use was significantly less among patients in postdetoxification treatment (12%) than among those who were not in treatment (50%) (Fisher exact test, $P = 0.002$). Patients in postdetoxification treatment also had less opioid use (12% vs 41.7%; Fisher exact test, $P = 0.02$), but not less cocaine or alcohol use.

The influence of variables on cannabis use at follow-up was analyzed using binary forward stepwise logistic regression. Only cannabis use at admission and VLNTX use during methadone detoxification added significance to the model (Table 1). In particular, patients who used cannabis and received NTX daily during methadone taper were 25 and 7 times less likely to use cannabis, respectively, at D1 and D7, compared with those who received methadone alone (Wald χ^2). Very-low-dose NTX treatment was a stronger predictor of nonuse of cannabis than was nonusing cannabis at admission (Table 1).

DISCUSSION

The proportion of patients who smoked cannabis after detoxification was significantly lower among those receiving VLNTX in addition to methadone taper. Cannabis use after discharge from inpatient detoxification was clinically significant in this sample because it was associated with increased opioid use and reduced engagement in outpatient treatment. These associations were not influenced by differences in sociodemographic and drug use characteristics.

Several factors may explain the effects of VLNTX treatment on cannabis use. Increased cannabis use was associated with more severe opioid withdrawal and craving at discharge. Cannabinoids attenuate the sympathetic hyperactivity associated with opioid withdrawal,[8] and opioid addicts may have attempted to mitigate withdrawal by using cannabis.[2,9] Activation of the cannabinoid CB1 receptor facilitates the reinforcing effects of opioids.[10] Thus, reduced cannabis use could promote abstinence from opioids. Conversely, opioid receptor activity may influence reduced cannabis use. It has been suggested that agonist action at the μ-opioid receptor increases cannabis reward and seeking behavior.[11] Naltrexone reduces the reinforcing effects of cannabis in nonhuman experiments[12] However, 50 mg NTX enhances subjective and reinforcing effects of cannabis in chronic users,[13] although a lower dose of NTX (12 mg) blunts these effects.[4] Thus, addition of VLNTX during detoxification may indirectly reduce cannabis use by reducing μ-opioid receptor activity, thereby reducing cannabis reward. There are indications that VLNTX may also act directly at the cannabinoid receptor. In preclinical studies, VLNTX increases analgesic and anticonvulsant effects of cannabis by acting at the CB1 receptor,[14,15] similar to effects observed with the CB1 receptor antagonist rimonabant.[16]

This study has several limitations. Cannabis use was not taken into account in the prospective randomization of subjects. It is possible that the association between VLNTX administration and reduced use of cannabis is accounted for by unmeasured confounds, although this likelihood is reduced by the randomized

TABLE 1. Binary Forward Stepwise Logistic Regression Model of Variables Predicting No Cannabis Use After Discharge From Inpatient Opioid Detoxification

Variable	W (*df*)	OR	95% CI	LR (*df*)	*P*
Day 1 follow-up (n = 96)					
Negative urine for cannabis at admission	4.7 (1)	4.4	4–14.5	10.6 (1)	0.03
VLNTX addition to detoxification	25.6 (1)	20.4	12.8–28.1	34.8 (2)	0.001
Day 7 follow-up (n = 61)					
Negative urine for cannabis at admission	4.3 (1)	4.7	1.1–11.7	12.2 (1)	0.02
NTX 0.250 mg addition to detoxification	7.6 (1)	9.8	4.1–12.3	19.2 (1)	0.001

W indicates Wald χ^2; *df*, degrees of freedom; OR, odds ratio; CI, confidence interval; LR, likelihood ratio of significance of the model.

assignment to treatment groups. Confounding by sociodemographic, drug use, or treatment variables is unlikely because cannabis users and nonusers did not significantly differ in such characteristics. Another potential confounder is the high attrition rate observed during the study, which could have led to selection bias. Such bias is unlikely because the patients lost to follow-up did not differ significantly in sociodemographic characteristics or drug use history from those who participated in this follow-up study. We also limited the sensitivity of our analyses by dichotomizing cannabis use as present or absent. However, this approach does not detract from the validity of the results.

Despite these limitations, this study supports the validity of our earlier findings, the first to show that opioid manipulation significantly reduced cannabis use in a clinical setting. Further investigations are needed to confirm the efficacy of VLNTX in reducing secondary cannabis use, improving the outcome of outpatient treatment, and as possible treatment for primary cannabis abuse and dependence.

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Concordance Between Measures of Functioning, Symptoms, and Change *Examining the GAF, CGI-S, CGI-C, and PANSS*

To the Editors:

The clinical implications of the Positive and Negative Syndrome Scale (PANSS)[1] are sometimes not readily apparent.[2] To give clinical meaning to PANSS ratings, past research has linked scores on the Clinical Global Impression of Severity (CGI-S) and change (CGI-C), both of which are single-item 7-point ratings, with the 30-item PANSS.[3,4] Those studies have shown, for example, that a CGI-S rating of "mildly ill" corresponds to a PANSS total score of approximately 58 and that a CGI-C rating of "minimal improvement" corresponds to a 19% PANSS total reduction.[3] This study aimed to (*a*) replicate the CGI and PANSS linkage, (*b*) elaborate by examining linkage between PANSS scores and the Global Assessment of Functioning (GAF) scale,[5] and (*c*) examine the correspondence of a 20% change on the PANSS total (ie, treatment response) with the other measures.

The GAF is based on a simultaneous rating of 3 domains of functioning (psychological, social, and occupational) that ranges from 1 (persistent danger of severely hurting self or others [eg, recurrent violence] *or* persistent inability to maintain minimal personal hygiene or serious suicidal act with clear expectations of death) to 100 (symptom absence and functioning in all areas). Global Assessment of Functioning judgments are thus complex,[6] and the 3 functioning domains may not be related.[6] Global Assessment of Functioning ratings are more highly correlated with symptom severity than with social or occupational status.[7–10] Past research reports that the GAF is weakly correlated with the PANSS[11] and Scales for the Assessment of Negative and Positive Symptoms,[12] but research is yet to link the GAF, CGI, and PANSS.

Data were analyzed from an international open-label clinical trial of long-acting injectable risperidone in recent-onset schizophrenia (n = 303).[13] Data on participants (n = 263, 86.8%) with complete GAF,[5] PANSS,[1] and CGI[14] ratings at all 4 study visits (baseline and weeks 6, 12, and 26) were examined. Like other PANSS linkage studies,[3,4] equipercentile linking was implemented to concord comparable percentile rank scores on each measure pairing.[15]

Results of equipercentile linking are plotted in Figure 1. The left column in Figure 1 presents the linkages of symptom and functioning measures, and the right column presents linkage of change measures. For example, in Figure 1A, the GAF (*y* axis) and PANSS total scores (*x* axis) linkage shows "superior functioning" (GAF 100–91) linked to a PANSS total of 66 (range, 60–73), whereas "major impairment" (GAF 40–31), which was only present at baseline, linked to a mean PANSS total of 99 (range, 96–103). In Figure 1B, CGI-S scores (*y* axis) of "mild" linked to a GAF score (*x* axis) of 61 (range, 49–74). In Figure 1C, CGI-S scores (*y* axis) of "mild" linked to PANSS score of 57 (range, 56–59).

Regarding change, for instance, in Figure 1D, CGI-C (*y* axis) ratings of "much improved" linked to a PANSS percentage change score of −25.5% (−22% to 29%). In Figure 1E, CGI-C (*y* axis) ratings of "much improved" linked to GAF percentage change score (*x* axis) of 138% (133%–141%) (eg, a person who entered the study with a GAF of 30 [serious impairment] and improved to 71 [slight impairment]).

The common standard for treatment response, a PANSS total 20% reduction, corresponded with a GAF percentage change (*x* axis) of 170% (163–180) (Fig. 1F) and with a CGI-C improvement of 2 (much improved).

DISCUSSION

The CGI and PANSS were more closely related to each other across visits than with the GAF. The GAF linkage may have been less concordant because of its complexity since it requires a simultaneous single rating of 3 domains.[6] Alternatively, unlike the CGI and PANSS, the GAF measures functioning that may reduce the linkage. To illustrate the possible utility of this linkage, consider that a PANSS total score at baseline of 70 corresponds with a GAF rating of 80 (some mild symptoms).

The current results partly replicate previous studies that link the CGI-S and PANSS[3,4] (detailed comparison including values of current and previous studies is available at http://faculty.biu.ac.il/~levins/sups/JCPlink2010.pdf). There was less agreement between current and previous studies on CGI-C and PANSS percent reduction (treatment response). In previous studies,[3,4] PANSS 20% reduction corresponded with "minimally improved," whereas in the current study, it corresponded with "much improved." This difference may be due to the higher level of baseline severity in the past studies,[3,4] that resulted in more scope for improvement and the very low dropout rate or the longer follow-up period in the current study.

A unique design feature of the current study is that GAF and CGI assessments preceded the PANSS in the case report form. In previous linkage research, CGI ratings followed the PANSS and may have been dependent on the more in-depth PANSS assessment.[4] This ordering effect may contaminate previous results that extrapolate between the CGI and PANSS. A strength of the current study was the low dropout rate (14%) and extensive 26-week follow-up period as compared with 6 weeks[3] and 8 weeks[4] in past research.

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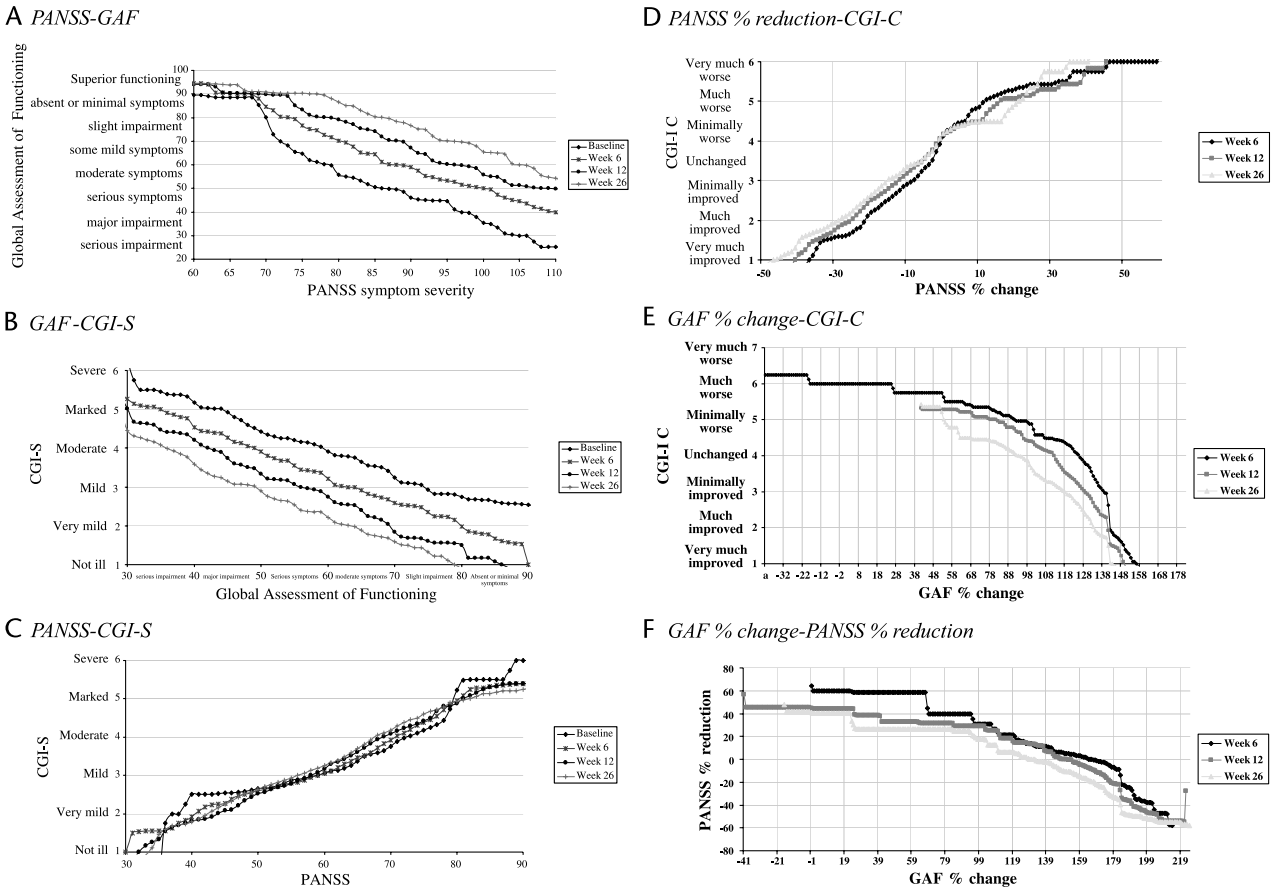

FIGURE 1. Linkages between the PANSS, CGI, and GAF on severity and change.

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What Is the Mechanism for Aripiprazole's Effect on Reducing Olanzapine-Associated Obesity?

To the Editors:

We read with great interest the article by Henderson and colleagues[1] in your journal, which reported that aripiprazole reduced olanzapine-associated overweight/obesity and hyperlipidemia in a 10-week placebo-controlled double-blind crossover study. This and their previous studies[1,2] provide a new way for controlling olanzapine- and clozapine-associated weight gain/obesity using another atypical antipsychotic, even without reducing the original olanzapine and clozapine doses, which is important particularly for treatment of refractory schizophrenia patients. The key issue is what are the mechanisms that underlie aripiprazole's effects on body weight? Henderson et al[1] proposed that aripiprazole's low histaminergic antagonism and 5-HT_{2C} agonist activity may contribute to its effect on reducing olanzapine-associated weight gain.

Several meta-analytical studies have indicated an association between histamine H1 antagonism properties in antipsychotic drugs and obesity adverse effects.[3,4] Consistent with these findings, both olanzapine and clozapine are potent H1 antagonists.[5] A recent study found that, correlated with body weight gain, olanzapine treatment significantly downregulated H1 receptor binding and mRNA expression in the rat hypothalamus; however, aripiprazole did not affect H1 receptor expression.[6] These results suggest that aripiprazole's effects in reducing olanzapine- and clozapine-associated weight gain/obesity are not likely to be via H1 receptors, although histaminergic antagonism is a main cause of olanzapine- and clozapine-associated weight gain/obesity.

We agree that 5-HT_{2C} receptors may play a role; however, it should also be noted that aripiprazole has only a moderate affinity to 5-HT_{2C} receptors.[7] Aripiprazole was developed as a potent dopamine D2 partial agonist, 5-HT_{1A} partial agonist, and also 5-HT_{2A} antagonist.[7] A recent study has reported that both aripiprazole and olanzapine affect 5-HT_{1A} receptor expression, but these changes are not correlated with body weight.[8] On the other hand, like aripiprazole, olanzapine and clozapine are 5-HT_{2A} antagonists.[5] Recent studies have suggested that aripiprazole is not a simple partial agonist, but a functionally selective drug that can act as a D2 agonist or D2 antagonist in different brain regions.[9,10]

We suggest that aripiprazole's D2 agonistic property may account partly for the effect of aripiprazole in reducing olanzapine-associated overweight/obesity. Atypical antipsychotics such as olanzapine may increase appetite through the dopamine-mediated reward pathway.[11] Dopamine D2 agonists have been reported to reduce food intake by acting in hypothalamic areas.[12]

Another possible mechanism of aripiprazole may be via the activation of the PI3K/Akt pathway. The PI3K/Akt pathway plays an important role in cellular proliferation, growth, and metabolism.[13] Overexpression of the pathway causes cancer, but defects in the pathway could induce metabolic disorders. The PI3K/Akt pathway plays a key role in the action of insulin via control of Glu4, which transports glucose into the cells.[14] The activity of the PI3K/Akt pathway in insulin-mediated Glu4 activation is impaired in olanzapine-associated obesity.[15] Aripiprazole may have an effect on the activation of the PI3K/Akt pathway via its agonistic effect on D2 receptors. In fact, D2 receptor agonist (bromocriptine) has been reported to increase the PI3K/Akt pathway activity.[16] It is possible that aripiprazole can restore the impairment of the PI3K/Akt pathway in insulin-mediated Glu4 activation caused by olanzapine so that the adverse effect of weight gain is reduced. Further studies on these mechanisms will improve our understanding and management of atypical antipsychotic-associated weight gain/obesity.

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