Mirtazapine for Alcohol Dependence: A Case Report

Sir: While alcohol dependence is highly prevalent, pharmacotherapy options for its management remain relatively limited[1] or underutilized.[2] Mirtazapine is indicated for the symptomatic treatment of depression. We report a case in which mirtazapine aided the treatment of a depressed alcoholic man, speculating that its 5-HT_3 antagonism may have contributed to its beneficial effect on his alcoholism.

Case report. Mr. A was a 59-year-old married white man with early-onset (prior to 25 years of age)[3] DSM-IV-TR alcohol dependence, consuming 26 ounces of Scotch daily over the past 5 years. He previously had experienced delirium tremens. His alcohol use was characterized by loss of control with legal charges and serious impairment in his work and marriage due to his drinking.

Mr. A was hospitalized in July 2004 after a suicide attempt following 6 months of daily depressed mood associated with anhedonia, decreased appetite, insomnia, poor concentration, and anergia. He also described ongoing uncontrollable worry and daily panic attacks and was using alprazolam at a dose of 0.5 mg/day. Prior trials of citalopram, paroxetine, sertraline, and fluoxetine adequate in dose and duration were ineffective in treating his mood and anxiety or altering his alcohol use. Prior residential addiction treatment resulted in only brief periods of abstinence. Liver function test results at admission were abnormal with a γ-glutamyl transpeptidase (GGT) level of 417 U/L (normal level, < 63 U/L), an aspartate aminotransferase (AST) level of 124 U/L (normal level, < 40 U/L), and an alanine aminotransferase (ALT) level of 184 U/L (normal level, < 60 U/L).

The patient was admitted to the hospital and detoxified via chlordiazepoxide taper (initially 50 mg/day) over 5 days. Motivational interviewing promoted further addiction treatment and abstinence. His suicidality resolved, but he remained overtly depressed with marked anxiety and sleep disturbance. Mirtazapine was introduced on day 4 of his hospitalization and titrated to 30 mg/day for management of his depression. Based on clinical observation and patient report, his mood improved and sleep normalized after 9 days in the hospital, allowing him to be followed thereafter as an outpatient.

At 3 months, Mr. A reported an absence of depression and insomnia, decreased anxiety, and continuous abstinence from alcohol and benzodiazepines with resolution of his liver function test abnormalities (GGT = 48 U/L, AST = 23 U/L, ALT = 22 U/L).

Mirtazapine has been used to aid alcohol withdrawal,[4,5] and this case may suggest that its use could extend to helping maintain abstinence in alcohol dependence, recognizing the limitations of drawing conclusions from a single case report. Mirtazapine may have addressed comorbid anxiety and sleep symptoms, known to predispose alcoholics to drinking relapse,[4–6] better than selective serotonin reuptake inhibitors (SSRIs) did in prior treatment trials.[7] In addition, the use of motivational interviewing, a known effective psychosocial intervention,[8] was most likely indispensable. An intriguing possibility, though, is that the receptor profile of mirtazapine may have targeted the serotonergic dysfunction that potentially differentiates early-onset from late-onset alcohol dependence.[3,9]

The disappointingly low clinical efficacy of SSRIs for alcohol dependence[1] may relate to genetically determined differences in serotonin transporter function that minimize potential therapeutic effects of SSRIs on alcohol intake.[9] Mirtazapine antagonizes central 5-HT_3 receptors[6] in a similar fashion to ondansetron, which has been purported to be beneficial in treating early-onset alcohol dependence.[8] 5-HT_3 receptors may play an important role in regulating mesocorticolimbic dopamine activity presumed to mediate alcohol's rewarding effects.[9] Antagonism of potentially up-regulated 5-HT_3 receptors may ameliorate serotonergic dysfunction, decrease reward, and regulate alcohol intake.[9]

Recognizing that alcohol intake should be avoided when taking mirtazapine (as it may increase drowsiness and dizziness), controlled trials of mirtazapine for alcohol dependence may be warranted.

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

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Efficacy of Quetiapine in Generalized Social Anxiety Disorder: Results From an Open-Label Study

Sir: The generalized form of social anxiety disorder is a highly prevalent psychiatric condition that causes persistent functional impairment.[1] Although selective serotonin reuptake inhibitors (SSRIs) have become the first-line treatment for social anxiety disorder,[2] these drugs do not always give adequate symptom relief, and side effects like initial increase of anxiety, gastrointestinal complaints, and sexual dysfunction can complicate their long-term use.

Animal models have shown that atypical antipsychotics also possess anxiolytic properties.[3–5] Recently, clinical reports have confirmed this anxiolytic profile.[5–11] The atypical antipsychotic olanzapine has shown favorable results in a small placebo-controlled trial in social anxiety disorder patients.[12] Quetiapine is an atypical antipsychotic registered for use in schizophrenia with a low propensity for extrapyramidal and endocrine side effects.[13] The objective of this study was to

Table 1. Primary and Secondary Outcome Variables in 13 Social Anxiety Disorder Patients Treated With Quetiapine: LOCF Analysis

Variable	Baseline, Mean (SD)	Endpoint, Mean (SD)	t	p[a]
Liebowitz Social Anxiety Scale				
Fear	42.62 (5.08)	28.08 (11.86)	4.56	.001
Avoidance	34.15 (7.56)	20.54 (9.61)	4.40	.001
Total	76.77 (10.25)	48.61 (21.07)	4.79	.0001
Brief Social Phobia Scale				
Fear	18.46 (3.41)	11.15 (6.36)	3.96	.002
Avoidance	17.00 (3.42)	9.62 (6.27)	4.48	.001
Physical	7.23 (2.77)	3.00 (2.55)	5.69	.0001
Total	42.69 (7.17)	23.77 (14.20)	5.02	.0001
Fear of Negative Evaluation Scale	35.54 (8.38)	20.61 (14.44)	4.13	.001
Social Phobia Inventory	42.23 (5.59)	22.85 (13.18)	5.22	.0001
Sheehan Disability Scale				
Work	7.46 (1.71)	3.69 (2.56)	4.95	.0001
Social	8.23 (1.17)	4.54 (2.60)	5.13	.0001
Family	4.77 (3.11)	2.54 (2.63)	2.34	.038
Hamilton Rating Scale for Anxiety	12.90 (4.07)	2.20 (1.93)	10.53	.0001
Clinical Global Impressions-Improvement scale	…	2.15 (1.07)	…	…
Quetiapine dose, mg/d	…	250.00 (54.01)	…	…
Weight, kg	82.40 (14.70)	84.30 (15.00)	2.51	.028
Plasma drug level, ng/mL	…	104.46 (136.8)	…	…

[a]Student t test (paired) using LOCF data. Analysis of Hamilton Rating Scale for Anxiety was based on completer data set.
Abbreviation: LOCF = last observation carried forward.

investigate the efficacy and tolerability of quetiapine, as monotherapy, in generalized social anxiety disorder patients.

Method. Thirteen patients with primary social anxiety disorder, generalized type (according to the DSM-IV and confirmed by the Mini-International Neuropsychiatric Interview[14]), who presented at the anxiety clinic at University Medical Center Utrecht, the Netherlands, were included in a 12-week open-label study. None of the patients had another current primary Axis I disorder or a primary personality disorder, with the exception of avoidant personality disorder. Eleven patients were drug-naive, and 2 were nonresponders to an adequate treatment with paroxetine. The Medical Ethical Review Committee of the University Medical Center approved the study. Data were collected from January to July 2004. Written informed consent was obtained from patients prior to inclusion.

Quetiapine was orally administered at flexible doses (150–300 mg/day). No other psychotropic medication was allowed during the study. Subjects were assessed at baseline and weeks 1, 3, 5, 8, and 12. The primary outcome parameters were the Liebowitz Social Anxiety Scale (LSAS)[15] and the number of responders. Responders were defined as those who had a score of ≤ 2 (much or very much improved) on the Clinical Global Impressions-Improvement scale.[16] Other outcome scales were the Brief Social Phobia Scale,[17] the Social Phobia Inventory,[18] the Fear of Negative Evaluation Scale,[19] the Hamilton Rating Scale for Anxiety,[20] and the Sheehan Disability Scale.[21] Vital signs (blood pressure, heart rate, and body weight) were measured at each visit, and plasma drug levels were assayed in weeks 8 and 12.

Results. The mean ± SD age of the patients (8 women and 5 men) was 33.2 ± 8.6 years. Ten patients (77%) completed the trial. Three patients discontinued prematurely due to adverse events (mainly sedation); 1 patient discontinued at week 8, and 2 patients dropped out after 1 week of treatment. Nine patients (69% of the last-observation-carried-forward sample) were considered responders. The only nonresponder who completed the trial appeared to be noncompliant (based on plasma drug level assays). This patient had previously also failed to respond to paroxetine. The baseline-to-endpoint scores dropped significantly for all outcome measures (Table 1). The total LSAS score decreased by 36.7%. The difference from baseline was significant as of week 3. The mean ± SD dose of quetiapine at endpoint was 250 ± 54 mg. Quetiapine was generally well tolerated. The most common adverse events were sedation, dry mouth, and dizziness. The mean plasma drug level at endpoint was 104 ± 137 ng/mL.

The response rate in this open-label study compares favorably with the results reported previously for SSRIs[22–24] and olanzapine.[12]

In conclusion, this study provides preliminary evidence for the efficacy of quetiapine in generalized social anxiety disorder. Currently, SSRIs are first-line treatment for patients with social anxiety disorder, but quetiapine might have a prospective role in social anxiety disorder patients who fail to respond to an adequate SSRI treatment. Larger controlled studies are warranted to better define the potential role of atypical antipsychotics in the treatment of generalized social anxiety disorder.

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

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Electroconvulsive Therapy for Coexistent Schizophrenia and Obsessive-Compulsive Disorder

Sir: There are now many studies showing the coexistence of schizophrenia and obsessive-compulsive disorder (OCD),[1] which often worsens the prognosis for remission of both illnesses. Likewise, it is well known that electroconvulsive therapy (ECT) is an effective treatment for schizophrenia patients who are resistant to antipsychotic drugs, and some studies suggest the same for OCD.[2] We report a case of comorbidity of both conditions successfully treated with ECT as evaluated by standardized clinical rating scales.

Case report. Mr. A, a 17-year-old male, had a history of excessive concerns about cleanness and contamination, accompanied by checking and reassurance-seeking rituals, for a period of 3 years. He was admitted to the psychiatry emergency room of a university hospital, brought by firemen who convinced him to leave his bedroom, where he had been for the past 9 months. During that time, he urinated in bottles and defecated on the floor and rarely bathed. Other complaints included diffuse paranoid ideation, poor insight, and affective instability, in addition to significant OCD symptoms.

After admission to an inpatient psychiatry ward, Mr. A continued to show isolation, paranoid ideas, obsessions, and compulsions. The patient met DSM-IV criteria for both schizophrenia and OCD, as assessed by the Portuguese version of the Clinical Version of the Structured Clinical Interview for DSM-IV.[3] Treatment consisted of pharmacotherapy (fluoxetine, haloperidol, risperidone, clomipramine, and carbamazepine) at various times with normally successful therapeutic doses, occupational therapy, and family and group psychotherapy. Despite all of these attempts, he showed no improvement during the first 3 months of hospitalization. Instead, he began to have new obsessive thoughts of hitting family members and staff, destroying furniture, and, finally, biting his tongue and pulling his penis out.

After the patient had been physically restrained or pharmacologically sedated most of the time for 2 weeks due to his hyperactivity and impulsivity, we decided to try ECT. Bitemporal stimuli were delivered bilaterally by a Thymatron Tm (Somatics, Lake Bluff, Ill.), DG-100% = 504 microcoulomb (brief-pulse) device. A total of 6 effective (generalized motor or electrographic seizures lasting more than 25 s and 30 s, respectively) ECT sessions were administered (twice a week) over a period of 3 weeks.

During the period of treatment with ECT, Mr. A was independently evaluated by 2 psychiatrists using the Brief Psychiatric Rating Scale (BPRS),[4] the Yale-Brown Obsessive Compulsive Scale (YBOCS),[5] and the Clinical Global Impressions scale (CGI).[6] In the few instances when assessments were not the same, a consensus rating was made. Aggressive, psychotic, and OCD symptoms markedly decreased on all rating scales employed: BPRS score decreased from 27 to 8; YBOCS score, from 50 to 16; and CGI score, from 6 to 2. The decrease following ECT was observed on all BPRS items, including those closely related to both psychotic and anxiety symptoms. Clomipramine and risperidone were administered after the treatment with ECT, which resulted in improvement in Mr. A's quality of life. A 6-month follow-up showed no relapse of the patient's positive psychotic symptoms, compulsions, or impulsivity, although some isolation and obsessive thoughts remained.

Pharmacologic treatment of comorbid schizophrenia and OCD generally includes selective serotonin reuptake inhibitors or tricyclic antidepressants along with an antipsychotic drug. In some reports of ECT in patients with either OCD or schizophrenia, the results were not as satisfactory, possibly because of technique, symptomatic differences, or differences in degree of illness.[7] Our results confirm a previous report[8] and suggest that ECT could be an option for the treatment of this comorbidity, even preceding medication, especially in cases in which the severity of the symptoms poses a serious threat to the patient's mental health and physical safety.

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

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Underpowered Repetitive Transcranial Magnetic Stimulation Might Not Be an Effective Antidepressant Treatment

Sir: Koerselman et al.[1] reported the results of a trial of repetitive transcranial magnetic stimulation (rTMS) for the treatment of depressive disorders. After 2 weeks, the improvement on the 17-item Hamilton Rating Scale for Depression (HAM-D) was not different between the active and the placebo arms of the study and in fact was very disappointing at 18.5% and 15.4%, respectively.

We agree with the authors that one explanation for the poor outcome was the low setting of the stimulation parameters, especially the use of just 80% of motor threshold. A recent review by Gershon et al.[2] showed that using intensities of ≥ 100%, using more pulses per session (≥ 1200), and continuing the treatment for more than 2 weeks were 3 factors associated with better response rates.

We would like to add our similarly disappointing experience with using a different set of stimulation parameters, which, in retrospect, appears to be underpowered as well. We wanted to replicate the results of an earlier, highly successful study[3] that used 1-Hz stimulation applied to the right dorsolateral prefrontal cortex for 120 pulses per session over 2 weeks. Instead of having a placebo arm, we compared the performance of the standard figure-of-eight coil (used in the majority of rTMS studies) with that of a round 9-cm coil (used by Klein et al.[3]). The effect of the 2 different coils has not been compared directly before.

Ethics committee approval was obtained, and patients signed informed consent forms. We randomly assigned 14 patients (mean age = 49.5 years; range, 26–71 years) with a mean HAM-D[4] score of 22.6 (range, 15–31) to 1 of the 2 treatments. Changes in HAM-D score were assessed by a rater who was blinded to the treatment parameters. Two patients in the round coil group did not complete the 10 sessions and were not included in the analysis. The mean change in HAM-D score in the 5 patients treated with the round coil was from 20.6 to 17.0 at the end of the treatment (a 17.5% drop). For the 7 patients treated with the figure-of-eight coil, the change was from 23.0 to 17.1 (a 25.6% drop). Only 1 patient achieved remission (HAM-D score < 8).

The difference between the 2 groups was not significant. More importantly, we interpret these changes as showing not clinically relevant improvement and not differing from the expected placebo-response rate. They are very similar to the placebo response rates in the studies by Koerselman et al.[1] (15.4%) and by Klein et al.[3] (22.1%) and would be even worse if we were to include the 2 dropouts, as they were showing no improvement. The study by Klein et al.[3] demonstrated a very good response rate of 46.9% in the rTMS group but did not include treatment-resistant cases, (although they were all inpatients). In contrast, all but 1 of the patients in our study were treatment resistant (having received at least 2 adequate unsuccessful courses of different classes of antidepressants), and a number of them had been referred to us for a "last resort" treatment. All but 1 were outpatients.

Our results add to the evidence that underpowered rTMS is not a strong antidepressant treatment, at least in treatment-resistant populations. Apart from our use of a very low number of impulses, we question, in retrospect, our choice of giving an antidepressant treatment for only 2 weeks. Future studies should explore higher settings given over at least 4 weeks, as suggested by Gershon et al.[2] Despite the small number of patients in our study, we have now decided to stop the trial and change the treatment parameters.

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Dr. Koerselman Replies

Sir: We thank Kirov et al. for their response to our article "A 3-Month, Follow-Up, Randomized, Placebo-Controlled Study of Repetitive Transcranial Magnetic Stimulation in Depression." We fully agree that conducting further research would make sense only if higher stimulation parameters than those in our study are used. Their data support this view. On the basis of our findings, however, we would also strongly advocate

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including a poststimulation follow-up period of at least 3 months. Our finding of a possible late effect, even after underpowered stimulation, is in need of replication, also with higher stimulation parameter settings. As a matter of fact, research on longer follow-up periods without breaking the blind may cause practical problems such as lessened motivation of patients to enter the study or the risk of loss to follow-up. Nevertheless, as Kirov et al. rightly state, useful lessons may be drawn from their and our experience.

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Low-Dose Risperidone and Quetiapine as Monotherapy for Comorbid Anxiety and Depression

Sir: Up to 80% of patients with generalized anxiety disorder (GAD) suffer from a comorbid mood disorder.[1] Atypical antipsychotics are frequently prescribed as off-label adjunctive treatment for GAD and major depressive disorder (MDD); however, no studies have demonstrated the effectiveness of these drugs as monotherapy.[2,3] Here, we present a case series describing the use of risperidone and quetiapine as monotherapy for GAD and MDD.

Method. Thirty-six patients (male and female, aged 21–79 years) with a DSM-IV diagnosis of GAD only (22 patients) or GAD with panic disorder (14 patients) were treated with either risperidone (N = 23) or quetiapine (N = 13). Of these patients, 27 suffered from comorbid MDD. Dosages were titrated upward until patients reported relief or had been treated for 2 weeks. Patients treated with risperidone were started at a dose of 0.125 mg p.o. q.h.s., which was increased by 0.125 mg/day to 0.25 mg and then by 0.25 mg/day to 0.5 mg. Patients treated with quetiapine were started at a dose of 25 mg p.o. q.h.s., which was increased by 25 mg/day to 100 mg and then by 50 mg/day to 300 mg. Anxiety and depressive symptoms (baseline and posttreatment) were evaluated using the Hamilton Rating Scale for Anxiety (HAM-A)[4] and a modified (2 anxiety items removed) Hamilton Rating Scale for Depression (HAM-D).[5]

Results. Four patients out of 36 dropped out: 2 were lost to follow-up, and 2 patients treated with risperidone refused posttreatment evaluation and were considered nonresponders. Mean ± SD baseline HAM-A scores were 22.84 ± 6.08 for all patients, 21.42 ± 5.53 for patients treated with risperidone, and 24.92 ± 6.45 for patients treated with quetiapine. Mean posttreatment HAM-A scores were 6.41 ± 5.30 ($t = 6.8$, $df = 31$, $p < .001$) for all patients, 5.68 ± 5.03 ($t = 4.9$, $df = 18$, $p < .001$) for patients treated with risperidone, and 7.46 ± 5.71 ($t = 4.7$, $df = 12$, $p < .001$) for patients treated with quetiapine. Mean baseline HAM-D scores were 23.06 ± 9.33 for all patients, 24.95 ± 10.01 for patients receiving risperidone, and 20.31 ± 7.79 for patients receiving quetiapine. Mean posttreatment HAM-D scores were 8.72 ± 5.84 ($t = 8.4$, $df = 31$, $p < .001$) for all patients, 6.37 ± 4.96 ($t = 5.6$, $df = 18$, $p < .001$) for patients treated with risperidone, and 12.15 ± 5.44 ($t = 8.0$, $df = 12$, $p < .001$) for patients treated with quetiapine.

The mean final daily dosages of risperidone and quetiapine were 0.21 ± 0.11 mg and 105.8 ± 93.1 mg, respectively. Of 19 patients receiving risperidone, 17 (89%) showed an improvement in HAM-A scores by at least 50%. Sixteen (89%) of 18 patients taking risperidone showed an improvement in HAM-D scores by at least 50%. (One patient had an initial HAM-D score of zero.) Of 13 patients taking quetiapine, 10 (77%) demonstrated an improvement in HAM-A scores by at least 50%, and 4 (31%) demonstrated improvement in HAM-D scores by at least 50%.

Our results show that risperidone and quetiapine are effective for GAD in doses far below those used for psychoses. An explanation for this may be that they have a higher affinity to 5-HT_2 than D_2 receptors. Risperidone occupies 5-HT_{2A} receptors at one tenth of the dose required for an equivalent occupation of D_2 receptors.[6] Similarly, quetiapine occupies 38% of 5-HT_{2A} receptors and 13% of D_2 receptors at a dosage of 150 mg.[7] The low D_2 receptor occupancy at this dose explains the low incidence of side effects in this case series.

Atypical antipsychotics are increasingly being used to augment the treatment of GAD and MDD without major psychotic disorders. The outcome of this case series offers intriguing preliminary evidence that low-dose monotherapy with risperidone or quetiapine is effective in this patient population. Further controlled studies are needed to confirm these findings. Of note, the risk of tardive dyskinesia with small doses of either risperidone or quetiapine is unknown in this group of patients. Therefore, until such risk is assessed, these drugs should not be used as first-line treatments for anxiety and panic.

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