Quetiapine for Hypersexuality and Delusional Jealousy After Stroke

To the Editors:

Hypersexuality and psychotic symptoms are occasionally associated with Parkinson’s disease, dopamine agonist therapy for Parkinson’s disease,6–8 dementia,6,7 and temporal lobe seizures,8 but rarely with stroke.6,8–11 Although some studies have shown that quetiapine is effective in treating psychosis and motor functions in Parkinson’s disease,12–17 as far as we know, there have not been any treatment response studies in the area of hypersexuality and psychosis after a stroke. We present a case in which hypersexuality and delusional jealousy after a stroke were successfully managed with quetiapine.

CASE REPORT

A 63-year-old right-handed man with Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition psychotic disorder due to a stroke, with delusions, was referred to our outpatient clinic in March 2005 for worsening psychotic symptoms. His main symptoms were hypersexuality and delusional jealousy. These symptoms troubled his wife very much.

He had been diagnosed with a right hemisphere infarction in the middle cerebral artery distribution in September 1991. Mild weakness of the left extremities developed, artery distribution in September 1991. Mild weakness of the left extremities developed, and his son was not his own). At the time, he did not receive any treatment because these symptoms were expressed intermittently.

In September 2004, his symptoms persisted and became aggravated (he repeatedly demanded sexual intercourse and doubted his wife’s chastity). Thus, treatment was started with haloperidol 0.75 mg/d, bupropion 100 mg/d, and flunitrazepam 1 mg at bedtime at another hospital. Haloperidol was titrated to 5 mg/d, bupropion was maintained at a dose of 100 mg/d, and flunitrazepam was titrated to 2 mg at bedtime. In November 2004, carbamazepine 200 mg/d was added and titrated to 400 mg/d. The dosage of antipsychotics could not be raised because his motor functions began to worsen due to extrapyramidal symptoms. His symptoms could not be controlled, and he was referred to our hospital in March 2005. Magnetic resonance imaging was obtained, and we could find no recent onset brain infarction or hemorrhage except for the right hemisphere old infarction in the M1 branch of the middle cerebral artery distribution. Magnetic resonance imaging showed large encephalomalacia in the right frontoparietal lobe and right basal ganglia of the middle cerebral artery territory except for some parts of the head of right caudate supposed to be the anterior cerebral artery territory.

On the Wechsler Adult Intelligence Scale, his IQ was 104, his Mini-Mental State Examination score was 26, and his Brief Psychiatric Rating Scale (BPRS) score was 53. (In our hospital, the BPRS score of admitted psychotic patients ranged from 38 to 63 and that of psychotic outpatients ranged from 25 to 40). These scores were measured by one psychologist in our hospital. The psychologist was not informed about any information associated with the dosing of medication.

We started treatment with quetiapine 50 mg twice a day and zolpidem 10 mg at bedtime. On the second day after treatment, his wife began to feel that his symptoms (demanding sexual intercourse and expressing delusional jealousy) had remarkably decreased. One month after treatment, his BPRS score was 42, and quetiapine was titrated to 125 mg/d. Four months after treatment, the BPRS score was 34. He developed no severe adverse effects including a worsening of motor functions, and his wife became more comfortable in living with him.

A review of literature suggests that hypersexuality and psychotic behavior are rare after cerebrovascular accident, but when such behavior does occur, the lesion is usually in the right hemisphere.18,19 and psychotic symptoms may occur immediately after a stroke or months to years later.20 Our patient also presented hypersexuality and delusional jealousy 2 years after the onset of a right cerebral infarction. As in Parkinson’s disease, a deterioration of motor functions is the main obstacle in managing geriatric stroke patients. Our case suggests that quetiapine is effective in treating hypersexuality and psychotic symptoms after a stroke, without a worsening of motor functions. We think that this case warrants further well-controlled research.

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Hypothermia in a Patient Receiving Risperidone and Paroxetine

To the Editors:

We describe a case of hypothermia in a patient taking risperidone in the absence of other causes of hypothermia. The introduction of paroxetine may have facilitated the development of hypothermia in this patient. Clinicians should be aware of the potential of risperidone to cause hypothermia as well as the drug interaction between risperidone and paroxetine, 2 commonly used agents in the elderly population.

CASE

A 79-year-old African American woman with a history of mild dementia presented to our emergency department with mental status changes, lethargy, and decreased oral intake for the past 2 weeks. She was accompanied by her daughters who provided collateral history. There was no history of chills, headache, shortness of breath, chest pain, cough, abdominal pain, diarrhea, constipation, nausea, vomiting, dysphagia, or choking on food. The patient denied any changes in urine color or dysuria. She lived in assisted living, used a walker to walk, and needed help with feeding, dressing, and managing her bills but, otherwise, interacted well with her helpers. Her medical history included hypertension, depression, dementia, and history of hallucinations. She had carotid surgery and bilateral hip replacement a few years ago. She had no known allergies, and her medications before admission included risperidone 0.25 mg orally BID, amlodipine 5 mg daily, galantamine hydrobromide 8 mg in the morning and 4 mg in the evening, docosate sodium 100 mg daily, celecoxib 200 mg daily, and calcium citrate 600 mg BID. Her primary care physician added paroxetine 10 mg daily for her depression 4 weeks before her presentation to the hospital. The patient had no history of alcohol or intravenous drug abuse.

On physical examination, her blood pressure was 129/67 mm Hg; pulse, 61 beats/min and regular; respiratory rate, 16 breaths/min; and rectal temperature, 33.4°C. She was lethargic but easily arousable and followed commands. Her mucous membranes were dry. She had normal breath sounds bilaterally, no jugular venous distension, and normal first and second heart sounds. Her abdominal examination revealed no tenderness or guarding; bowel sounds were normal. Neurological examination showed equal pupils which were reactive to light, extraocular movements were intact. Her cranial nerves were normal. Focal motor deficits were noted. Muscle strength was 4 of 5 bilaterally in the upper and lower extremities, and sensation to light touch was intact. There were no signs of rigidity or cerebellar signs, and her reflexes were normal.

Laboratory evaluation on admission revealed normal serum chemistries, mild anemia and thrombocytopenia (hemoglobin 12.8 g/dL, platelet count 122,000/mm³), and a normal thyroid-stimulating hormone. A computed tomography scan of the brain showed mild atrophy with no evidence of acute bleeding or stroke. Her chest radiograph was normal with no infiltrates or effusions. Urine analysis was normal, and urine toxicology screen was negative. A lumbar puncture was performed demonstrating normal protein and glucose levels, 1 red blood cell, and no white blood cells or organisms. Blood, urine, and cerebrospinal fluid cultures grew no organisms.

Paroxetine, risperidone, and galantamine were discontinued and the patient received warming blankets and intravenous fluid hydration. Her oral temperature returned to 36.9°C with no external warming 40 hours after admission, and her mental status improved.

Mild hypothermia is most likely to be responsible for this patient’s symptoms. Hypothermia has been reported in association with risperidone. The patient had been receiving risperidone for 6 months before this hospital admission with no previous episodes of hypothermia. The introduction of paroxetine may have raised risperidone levels and caused hypothermia in our patient.

DISCUSSION

The hypothalamus is responsible for thermal regulation. Hypothermia (defined as core body temperature of less than 35°C) can be caused by accidental cold exposure or dysfunction of hypothalamic thermoregulation.1 An underlying illness is often the predisposing factor; this includes hypothyroidism, heart failure, uremia, hepatic encephalopathy, stroke, shock or sepsis, hypoglycemia, or burns.1 None of these medical conditions are present in our patient, as evidenced by her laboratory values, computed tomography scan results, and negative blood, urine, and cerebrospinal fluid cultures.

Medications that can cause hypothermia include sedative-hypnotics, alcohol, antithyroid medications, narcotics, and typical antipsychotic medications such as haloperidol and phenothiazines.1 Hypothermia has been reported as an adverse effect of the atypical antipsychotic medications quetiapine, olanzapine, and risperidone.2–4 Cases of risperidone-induced hypothermia have been reported by Brevik and Farver5 and by Razaq and Samma.6

Risperidone is an atypical antipsychotic medication that is used in the treatment of both positive and negative symptoms of schizophrenia. Risperidone is a serotonin 5HT2 and dopamine D2 receptor antagonist.7 It is metabolized in the liver mainly by cytochrome P450 (CYP)2D6 to form 9-hydroxyrisperidone (9-OH risperidone), which also blocks 5HT2 and D2 receptors. Combined serum levels of risperidone and the active metabolite 9-OH risperidone are responsible for the therapeutic effects of risperidone.8 Recent studies


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indicate that risperidone may aid in the treatment of depression by augmenting the activity of selective serotonin reuptake inhibitors, including paroxetine. Risperidone and paroxetine interaction can lead to weight gain, priapism, and rarely to serotonin syndrome.

Paroxetine is a substrate and inhibitor of CYP2D6. Metabolism by the CYP2D6 enzyme is saturable at usual doses of paroxetine in 90% of patients. Paroxetine is known to raise the plasma concentration of risperidone and 9-OH risperidone. When paroxetine was added to risperidone therapy, Spina et al. observed a 45% increase in mean risperidone plus 9-OH risperidone (risperidone active moiety) concentrations in 10 CYP2D6 extensive metabolizers. Our patient was also receiving galantamine, a competitive inhibitor of acetylcholinesterase. Galantamine is metabolized via CYP2D6 and CYP3A4 but it does not inhibit those enzymes. Coadministration of galantamine and risperidone does not increase the serum concentration of risperidone active moiety. Paroxetine can raise galantamine levels by inhibiting CYP2D6 leading to a 40% increase in its bioavailability. Galantamine has been reported to cause hypothermia in animal models, but there are no reported cases of galantamine-induced hypothermia in humans in the English literature. In organophosphate poisoning, which usually leads to irreversible inhibition of acetylcholinesterase, humans usually have a hyperthermic response compared with the hypothermic response noted in rodents. Galantamine potentially may have contributed to this patient’s hypothermia because of the pharmacokinetic interaction of galantamine and paroxetine or to a possible pharmacodynamic interaction between galantamine and risperidone. However, accumulated clinical data in humans do not support this hypothesis. The decrease in oral intake might be a result of hypothermia and not the cause of it, especially since the patient had no clinical signs of dehydration.

To our knowledge, this is the sixth reported case of risperidone-induced hypothermia. The drug interaction between paroxetine and risperidone may also have been a factor in the development of hypothermia in this patient. Clinicians should take note of this interaction between these 2 agents that are commonly used in the elderly population.

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Impact of Orally Disintegrating Olanzapine on Use of Intramuscular Antipsychotics, Seclusion, and Restraint in an Acute Inpatient Psychiatric Setting

To the Editors:

Intramuscular (IM) conventional antipsychotics have long been used to manage agitation and aggression in the psychiatric inpatient setting. Although generally effective, these preparations...
have multiple drawbacks, both in terms of side effects and as a consequence of their route of administration. In addition to these factors, treatment invoking the principle of the “least restrictive environment or intervention” has become generally accepted in the psychiatric community. This ethical standpoint serves as a compromise between individual rights and severely mentally ill patients’ need for treatment, particularly in cases in which impaired reality testing or impulse control may be associated with potentially dangerous behavior. From this perspective, it is important to reduce the use of both invasive routes of medication administration and seclusion and restraint. Finally, a reduction in the number of violent outbursts and episodes of seclusion and restraint may improve patient and staff morale.

Recently, literature has emerged showing that, in patients willing to take them, oral atypical antipsychotics are as effective as IM conventional antipsychotics in treating acute psychotic agitation. We report on the use of a rapidly dissolving oral formulation of an atypical antipsychotic (olanzapine Zydis; Zyprexa, Eli Lilly and Co, Indianapolis, IN; Zydis, Cardinal Health Pharmaceutical Technologies and Services, Somerset, NJ) on a high-intensity acute inpatient ward.

In November 2002, the psychiatric intensive care unit (PICU) at the West Los Angeles Veterans’ Affairs Medical Center (VAMC) replaced 5 mg oral haloperidol with 10 mg olanzapine Zydis (an oral, rapidly disintegrating “wafer” formulation) as the “as needed” oral antipsychotic of choice for agitation. We hypothesized that the availability of oral olanzapine Zydis would reduce the use of IM antipsychotics in this setting. We also examined the impact of olanzapine Zydis on the use of seclusion and restraint.

In a retrospective chart review, we collected data on the use of p.r.n. IM antipsychotics, seclusion, and restraint for all patients admitted to the PICU at the VAMC in West Los Angeles in the 6 months before the introduction of olanzapine Zydis to the ward formulary (the “PRE” group) and in the 6 months after its introduction (the “POST” group). The PICU is a locked, 12-bed psychiatric “crisis” unit for the most acutely ill psychiatric patients treated at the West Los Angeles VA. The study protocol was approved by the West Los Angeles VAMC Institutional Review Board. An exemption to the requirement for informed consent was obtained by excluding identifying data and by other security measures to protect confidential patient information.

### Patient Demographics and Diagnoses

The demographic and diagnostic information for the 2 groups are presented in Table 1. For purposes of analysis, diagnoses assigned at the time of discharge or transfer were divided into 6 categories: (1) primary psychotic disorders (ie, schizophrenia and schizoaffective disorder), (2) substance-induced psychotic disorder and psychotic disorder not otherwise specified, (3) type I bipolar disorder, (4) dementia or delirium, (5) substance use disorders (excluding substance-induced psychotic disorder), and (6) all other diagnoses.

### Administration of Intramuscular and Oral Antipsychotics for Acute Agitation

The data regarding the number of administrations of emergent IM conventional antipsychotics for both study groups and of olanzapine Zydis in the POST group are shown in Table 1. There were no significant differences between the 2 groups.

### Seclusion and Restraint

In the PRE group, 16 patients (8.8%) were placed in seclusion, and 13 (7.2%) were placed in restraints. In the POST group, 16 patients (9.4%) were placed in seclusion, and 12 (7.0%) were placed in restraints. There were no significant differences between the 2 groups.

### DISCUSSION

The results of this study do not support our hypothesis that the availability of olanzapine Zydis to the ward formulary; POST, patients admitted in six-month period after addition of olanzapine Zydis to the ward formulary; N/A, not applicable; first-line, before administration of olanzapine Zydis; second-line, after administration of olanzapine Zydis (for a given episode of agitation).

### TABLE 1. Patient Demographics, Diagnoses, and Use of p.r.n. Antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>PRE Group (n = 181)</th>
<th>POST Group (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>46.6 ± 8.5</td>
<td>47.5 ± 9.2</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>166 (92)</td>
<td>161 (94)</td>
</tr>
<tr>
<td>Length of stay, mean ± SD, d</td>
<td>7.4 ± 8.7</td>
<td>8.2 ± 10.2</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>78 (43)</td>
<td>69 (40)</td>
</tr>
<tr>
<td>African American, n (%)</td>
<td>75 (41)</td>
<td>87 (51)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>20 (11)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>8 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Primary psychotic disorder, n (%)</td>
<td>44 (24.3)</td>
<td>46 (26.9)</td>
</tr>
<tr>
<td>Substance-induced psychosis/psychosis not otherwise specified, n (%)</td>
<td>19 (10.5)</td>
<td>15 (8.8)</td>
</tr>
<tr>
<td>Bipolar disorder, n (%)</td>
<td>22 (12.2)</td>
<td>15 (8.8)</td>
</tr>
<tr>
<td>Dementia/delirium, n (%)</td>
<td>7 (3.9)</td>
<td>7 (4.1)</td>
</tr>
<tr>
<td>Substance use disorder, n (%)</td>
<td>62 (34.3)</td>
<td>66 (38.6)</td>
</tr>
<tr>
<td>All emergent IM conventional antipsychotics, n (%)</td>
<td>27 (14.9)</td>
<td>26 (15.2)</td>
</tr>
<tr>
<td>“First-line” emergent IM conventional antipsychotics, n (%)</td>
<td>N/A</td>
<td>20 (11.7)</td>
</tr>
<tr>
<td>“Second-line” emergent IM conventional antipsychotics, n (%)</td>
<td>N/A</td>
<td>9 (5.3)</td>
</tr>
<tr>
<td>Emergent oral olanzapine Zydis, n (%)</td>
<td>N/A</td>
<td>37 (21.6)</td>
</tr>
</tbody>
</table>

PRE indicates patients admitted in 6-month period before addition of olanzapine Zydis to the ward formulary; POST, patients admitted in six-month period after addition of olanzapine Zydis to the ward formulary; N/A, not applicable; first-line, before administration of olanzapine Zydis; second-line, after administration of olanzapine Zydis (for a given episode of agitation).
a rapidly disintegrating formulation of an atypical antipsychotic for emergent use would reduce the use of IM antipsychotics or of seclusion or restraint in an acute inpatient psychiatric setting. In comparison with a similar patient population admitted before the addition of olanzapine Zydis to the ward formulary, the study group demonstrated no change in use of IM antipsychotics, seclusion, or restraint. While this may suggest that the introduction of olanzapine Zydis to the ward formulary did not reduce the use of more restrictive interventions, the lack of a quantitative measurement of illness severity (eg, a Global Assessment of Functioning score at the time of admission) precludes drawing any firm conclusions regarding the impact or lack of impact of the availability of p.r.n. olanzapine Zydis on these outcome measures. In other words, it is possible that a difference in overall illness severity between the 2 groups may have obscured any potential benefits such as reduced use of IM antipsychotics, seclusion, or restraint. However, this possible explanation seems less likely when considering the lack of any known changes in the VA population accessing services during the 12 months of the study and the similar demographics and distribution of diagnoses in the 2 groups.

This study has several limitations. Patients must agree, if only by assent, to take any oral medication. Patients who are extremely ill or acutely agitated may refuse oral medications, precluding this treatment option and necessitating IM medication when agitation requires emergent medication. We did not assess the role of patient refusal in the selection of interventions for emergent agitation. Similarly, we did not address the role of nursing staff’s clinical judgment regarding these interventions.

Another limitation of the study is its naturalistic design. We did not address variables such as standing antipsychotic or mood-stabilizing medication orders or the use of p.r.n. oral benzodiazepines. In fact, in the acute inpatient setting studied here, oral benzodiazepines, primarily lorazepam, are used frequently on a p.r.n. basis for anxiety and agitation. It is possible that those who did not respond to benzodiazepines had a more severe level of agitation more likely to require IM medication. Thus, there may have been a tradeoff between use of benzodiazepines and olanzapine Zydis after the introduction of the latter. A study in which only antipsychotics were used might provide a more definitive comparison of the utility of oral atypical antipsychotics versus IM medications in controlling severe agitation.

It should also be remembered that although olanzapine Zydis dissolves rapidly in the mouth, its absorption occurs via the gastric mucosa. Therefore, its onset of action is equivalent to the tablet form. This relatively slow onset of action (peak plasma level at 6 hours after administration) may in part explain the lack of effect seen for olanzapine Zydis in reducing emergent IM use and seclusion and restraint in the present study. It is possible that IM antipsychotics, seclusion, or restraint was used before the onset of the clinical effect of olanzapine Zydis.

The use of IM atypical antipsychotics, such as olanzapine and ziprasidone, both of which have been recently approved for acute use in the United States, would avoid this pharmacokinetic disadvantage of oral olanzapine while maintaining atypical antipsychotic efficacy. These agents greatly reduce the frequency of many of the adverse reactions seen with conventional antipsychotics, but obviously not those consequent to the IM route of administration. Nevertheless, these agents may address the acute treatment needs of patients too agitated to benefit from an oral agent.

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Altered Expression of Myeloperoxidase Precursor, Myeloid Cell Nuclear Differentiation Antigen, Fms-related Tyrosine Kinase 3 Ligand, and Antigen

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CD11A Genes in Leukocytes of Clozapine-treated Schizophrenic Patients

To the Editors:

Clozapine is an atypical antipsychotic drug that has been found to be superior in the treatment of schizophrenia resistant to conventional medication. Its use is, however, limited by the associated risk of agranulocytosis in approximately 1% of the patients. The exact pathogenesis of clozapine-induced agranulocytosis is still unclear. Several mechanisms such as immune-mediated cytolysis and triggering of apoptosis or cytotoxicity have been suggested to cause depletion of granulocytes. In addition, clozapine is metabolized to the stable metabolites demethyl-clozapine and clozapine N-oxide. Therefore, not only the parent compound itself but also its metabolites may be toxic. Agranulocytosis could hence be a complex entity with involvement of several molecular mechanisms.

We investigated the effect of clozapine on gene expression in granulocytes by performing a microarray analysis on RNA isolated from the blood leukocytes of schizophrenic patients who started clozapine treatment for the first time. In addition, the gene expression pattern was compared in vitro between clozapine-treated and nontreated granulocytic human promyelocytic leukemia (HL-60) cells. We then performed a quantitative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis to validate the biologically interesting changes in gene expression at 5 different time points of clozapine treatment and in the lymphocytes of clozapine-treated patients. In the patient leukocytes, quantitative RT-PCR analysis was also used to reveal differences in gene expression at 5 different time points of clozapine treatment. A detailed description of all the procedures can be requested from the authors. Two-tailed nonlinear equation model Student t tests were used to evaluate the fold changes in gene expression, and significance was defined as P less than 0.05.

Twenty-four of the 588 genes analyzed showed a different expression in the clozapine-treated cells compared with the nontreated HL-60 cells. A list of genes with altered expression is available from the authors upon request. For quantitative RT-PCR analysis, we selected 4 of these genes, because they had been implicated in the maturation or apoptosis of granulocytes for quantitative RT-PCR analysis. Two genes, Fms-related tyrosine kinase 3 ligand (FLT3LG) and myeloperoxidase precursor (MPO), showed down-regulated expression; whereas 2 genes, myeloid cell nuclear differentiation antigen (MNDa) and antigen CD11A, lymphocyte function–associated antigen 1 (ITGAL), were overexpressed after treatment with clozapine.

Tables 1A and B show the expression profiles of selected genes in the HL-60 cells and in the mononuclear leukocytes of the clozapine-treated patients. Enough RNA could not be extracted from the granulocytes of individual patients to allow RT-PCR analysis. We therefore pooled the samples at each time point. Tables 1C and D demonstrate the alterations in gene expression. Myeloperoxidase precursor gene was significantly underexpressed and MNDa overexpressed already 3 hours after drug intake, resembling the kinetics of altered gene expression seen in the HL-60 cells. Moreover, both genes remained down-regulated or up-regulated after 3 days, 2 months, and 4 months, respectively. Also, the FLT3LG gene showed linear down-regulation at all time points but less significantly. In contrast, the ITGAL gene was up-regulated after 3 hours but down-regulated at 3 days and 2 months, yet up-regulated again at 4 months.

By using the cDNA microarray technique, we could identify 4 genes implicated in the maturation or apoptosis of granulocytes that displayed altered expression. Because the respective changed expression profiles of the MPO and MNDa genes persisted in a linear curve through all time points up until four months, these gene alterations may have significance in clozapine-induced agranulocytosis. It is noteworthy that most clozapine-induced agranulocytosis occurs within 3 months of starting treatment. Also, the findings in the HL-60 cells supported this observation. As the patients used other...
antipsychotics including olanzapine, their involvement in the results cannot be excluded because we did not have a control group. The similar kinetics in the patient lymphocytes, where clozapine was started for the first time, and in the clozapine-treated HL-60 cells, however, supports a role of clozapine in the altered gene expression pattern. Furthermore, the recent findings point toward a unique role of clozapine in these alterations.\textsuperscript{4,5}

A lower expression of MPO gene in the granulocytes may be caused by its direct inhibition of MPO gene transcription by clozapine. Alternatively, clozapine treatment may select for subclones of granulocytes with low natural MPO expression, whereas cells with high expression of MPO are eliminated by nitrenium ion toxicity. Immunodestruction of leukocytes, which are antigenically modified by binding of clozapine metabolites, should still be considered a pathogenetic event in agranulocytosis.\textsuperscript{6–8}

Our observations in this preliminary study suggest that the expression of MPO and MND\(\text{A}\) genes is altered in granulocytes after clozapine administration. This may have some bearing on the clozapine-induced hematotoxic reaction in schizophrenic patients. The altered gene expression patterns of the FLT3LG and ITGAL genes may also suggest their involvement.

\begin{table}
\centering
\caption{Kinetics of altered expression of the MPO, MND\(\text{A}\), FLT3LG, and ITGAL genes (shown as fold changes) after treatment with clozapine in HL-60 cells (\textit{A}), in mononuclear leukocytes of individual schizophrenic patients (\textit{B}), in pooled RNA (8 individuals) from mononuclear leukocytes (\textit{C}), and from granulocytes (\textit{D}) quantitated by real-time RT-PCR.}
\begin{tabular}{lllll}
\hline
 & MPO & MNDA & FLT3LG & ITGAL \\
\hline
\textit{A. HL-60 cells} & & & & \\
3 d, cDNA & 0.179 & 2.116 & 0.182 & 1.97 \\
3 d, RT-PCR & 0.036 & 5.526 & 0.606 & 0.637 \\
\hline
\textit{B. Mononuclear leukocytes} & & & & \\
Patient 1 & & & & \\
3 h & 0.991 & 1.116 & 0.8154 & 1.5832 \\
3 d & 0.9645 & 0.987 & 0.6875 & 1.3337 \\
Patient 2 & & & & \\
3 h & 0.9865 & 0.841 & 1.30259 & 0.5719 \\
3 d & 0.9638 & 0.3941 & 0.99312 & 0.4084 \\
Patient 3 & & & & \\
3 h & 0.9895 & 2.797 & 0.80501 & — \\
3 d & 0.9769 & 1.969 & 0.6992 & — \\
Patient 4 & & & & \\
3 h & 0.976 & 0.563 & 0.9146 & 1.272 \\
3 d & 0.9656 & 1.032 & 0.7764 & 1.247 \\
Patient 5 & & & & \\
3 h & 0.9406 & 1.055 & 0.84156 & 0.971 \\
3 d & 0.97518 & 1.056 & 0.52967 & 0.976 \\
Patient 6 & & & & \\
3 h & 0.9984 & 1.028 & 0.396 & 1.522 \\
3 d & 0.9709 & 1.055 & 0.489 & 1.4408 \\
Patient 7 & & & & \\
3 h & 1.015 & 1.214 & 0.8014 & 2.583 \\
3 d & 1.0417 & 1.195 & 0.5985 & 2.8679 \\
Patient 8 & & & & \\
3 h & 0.9839 & 1.047 & 0.8607 & 1.508 \\
3 d & 0.9748 & 0.906 & 1.4894 & 0.943 \\
P for patients 1–8 for 3 h & 0.0446* & 0.2057 & 0.0556 & 0.0589 \\
P for patients 1–8 for 3 d & 0.0281* & 0.3214 & 0.7367 & 0.1549 \\
\hline
\textit{C. Pooled RNA from mononuclear leukocytes} & & & & \\
3 h & 0.98 & 1.06 & 0.92 & 0.88 \\
3 d & 0.96 & 1.12 & 0.82 & 0.92 \\
2 mo & 0.84 & 0.74 & 0.92 & 1.23 \\
4 mo & 0.74 & 1.68 & 0.83 & 4.02 \\
P & 0.061 & 0.249 & 0.194 & 0.009* \\
\hline
\textit{D. Pooled RNA from granulocytes} & & & & \\
3 h & 0.76 & 1 & 0.967 & 1.007 \\
3 d & 0.599 & 1.037 & 0.662 & 0.947 \\
2 mo & 0.521 & 1.044 & 0.602 & 0.939 \\
4 mo & 0.5 & 2.85 & 0.82 & 6.46 \\
P & 0.0018* & 0.0002* & 0.2010 & 0.0757 \\
\hline
\end{tabular}
\end{table}

*Significant difference at \(P < 0.05\) by \(t\) test.
are important enzymes in the metabolic inactivation of neurotransmitters, including dopamine, norepinephrine, and serotonin. A common functional polymorphism at codon 158 in the gene controlling COMT results in substantial differences in enzyme activity: the Met allele is associated with low enzyme activity and the Val allele, with high activity. The MAOA gene, located on the X chromosome, is associated with a 30-base pair variable number tandem repeat located in the promoter that affects enzyme activity. The 3.5 and 4 repeat alleles confer high enzyme activity, whereas the 3 and 5 repeat alleles confer low activity. The status of the 2 repeat allele is unclear, but some investigators have classified it as low activity based on its short length.

Illi et al examined the relationship between COMT and MAOA genotypes and response to treatment in 94 schizophrenic patients receiving a first generation antipsychotic. The low activity (Met/Met) COMT genotype was significantly more common in nonresponders. Although MAOA genotype alone did not differentiate between the responders and nonresponders, significantly fewer subjects with both the low activity COMT and MAOA genotypes were responders.

We examined the relationship between COMT and MAOA genotypes and response to treatment in a combined sample of patients with schizophrenia or schizoaffective disorder from 2 randomized, double-blind studies conducted at the same facility, using very comparable procedures, assessments, and schedules. Volavka et al compared clozapine, haloperidol, olanzapine, and risperidone in treatment resistant patients (Study 1) and Krakowski et al compared olanzapine and clozapine to haloperidol in persistently violent patients (Study 2). The COMT and MAOA genotypes were determined for 108 (Study 1, 58/Study 2, 50) and 106 participants (Study 1, 60/Study 2, 46), respectively. Both genotypes were in Hardy-Weinberg equilibrium in the sample. Because genotyping was not initiated at the beginning of either study, the genotyped subsets were not necessarily representative of the larger study samples from which they were drawn. Most participants were men (Study 1, 80%; Study 2, 86%) and African American (Study 1, 54%; Study 2, 58%). Mean duration of participation in the 2 studies was 10.7 weeks (SD, 3.7 weeks). Treatment response was measured in terms of change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to end point. Participants showing a reduction of at least 20% from baseline were classified as “responders.” Mean PANSS change (baseline-end point) did not differ significantly between studies (F = 0.97, df = 1, 102; P = 0.327). However, more of the genotyped participants were classified as responders in Study 1 (44.3% vs 26% in Study 2; \( \chi^2 = 3.98, df = 1, P = 0.046 \)).

Table 1 shows the mean PANSS changes and numbers of responders and nonresponders as a function of genotypes. Analysis of covariance using baseline severity and study as covariates revealed no significant difference among COMT genotypes in either mean change in PANSS (F = 0.05, df = 2, 102; \( P = 0.621 \)) or number of responders (\( \chi^2 = 0.24, df = 2, P = 0.888 \)). Although the L/L genotype was more than twice as frequent in nonresponders as compared with responders, the effect was not significant. To facilitate comparison with Illi et al, we contrasted L/L subjects with H/H and H/L combined. Again, no significant differences were found, either on mean change in PANSS (F = 0.51, df = 1,104; P = 0.475) or number of responders (\( \chi^2 = 0.13, df = 1, P = 0.722 \); odds ratio, 0.797; 95% confidence interval, 0.228–2.784).

Three alleles (2, 3, and 4) of the MAOA gene promoter polymorphism were observed in this sample. The 3 and 4 alleles constituted approximately 46% and 49%, respectively, of the observed alleles. We designated subjects with the 3-repeat low-activity allele(s) as “Low MAOA” and all others as “High MAOA.” There were no significant differences between Low and High MAOA groups in change in PANSS (F = 0.16, df = 1,102; P = 0.690) or number of responders (\( \chi^2 = 1.95, df = 1, P = 0.163 \)).

The small number of Low COMT subjects precluded a valid test of the MAOA × COMT interaction. Change in PANSS total score was greatest in
TABLE 1. COMT and MAOA Genotypes and Response to Treatment (Baseline-End Point)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Change in PANSS total*</th>
<th>Nonresponders, n (%)</th>
<th>Responders, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L/L</td>
<td>5.05 (15.72)</td>
<td>9 (69.2)</td>
<td>4 (30.8)</td>
</tr>
<tr>
<td>L/H</td>
<td>2.72 (17.75)</td>
<td>38 (65.5)</td>
<td>20 (34.5)</td>
</tr>
<tr>
<td>H/H</td>
<td>7.38 (14.54)</td>
<td>23 (62.2)</td>
<td>14 (37.8)</td>
</tr>
<tr>
<td>MAOAa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3.02 (15.82)</td>
<td>40 (70.2)</td>
<td>17 (29.8)</td>
</tr>
<tr>
<td>Low</td>
<td>5.70 (18.79)</td>
<td>28 (57.1)</td>
<td>21 (42.9)</td>
</tr>
<tr>
<td>COMT High/MAOA High</td>
<td>2.05 (16.17)</td>
<td>35 (71.4)</td>
<td>14 (28.6)</td>
</tr>
<tr>
<td>COMT Low/MAOA Low</td>
<td>5.39 (18.33)</td>
<td>23 (54.8)</td>
<td>19 (45.2)</td>
</tr>
<tr>
<td>COMT Low/MAOA High</td>
<td>10.25 (12.12)</td>
<td>4 (66.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>COMT Low/MAOA Low</td>
<td>−0.025 (10.82)</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
</tr>
</tbody>
</table>

*Mean (Standard Deviation).

aMAOA “High” genotype includes subjects with one or more copies of the 4 alleles; all other MAOA genotypes were classified as “Low.”

bCOMT “High” genotype includes subjects with at least one copy of the high activity (Val) allele. COMT “Low” genotype includes only low activity (Met) homozygotes.

subjects with Low COMT and High MAOA genotype (Table 1), but this difference was not statistically significant ($F = 1.73, df = 1, 98; P = 0.191$).

We were unable to confirm the results reported by Illi et al.4 In this sample, neither the COMT nor MAOA polymorphism had any significant effect on response to antipsychotic treatment. However, all of Illi et al’s subjects were treated with a first generation antipsychotic as compared with 25% of our subjects. Antipsychotic medications differ in dopamine receptor affinity, with clozapine and olanzapine binding more loosely to and releasing more rapidly from D2 receptors than haloperidol and risperidone.7 As a result, pharmacogenetic associations with treatment response might vary across medications. Therefore, we also analyzed the relationship between COMT and MAOA genotypes and change in PANSS scores, contrasting subjects who received clozapine or olanzapine versus those who received haloperidol or risperidone. Analyses of covariance using treatment duration and ethnicity as covariates revealed no significant genotype × medication interactions.

The studies differed in other ways that also might have contributed to the discrepant results. Illi et al based their determination of treatment response on retrospective evaluation of hospital records, personal medical history, and a personal interview but did not quantify change in psychopathology. In contrast, we prospectively measured change in psychopathology with the PANSS and defined treatment response as a minimum 20% reduction from baseline in a randomized clinical trial. The COMT L/L genotype was comparatively rare in our ethnically heterogeneous sample. Furthermore, our analyses combined the results of 2 studies that differed in patient eligibility criteria, baseline symptom severity, and other aspects that may have increased variance and confounded the results of our comparisons. Our sample combined patients with treatment resistance5 and persistent aggression,6 perhaps confounding pharmacogenetic phenotypes. Resolution of the question of how COMT and MAOA genotypes may be related to antipsychotic treatment response will require a prospective study designed with sufficient power to compare response to typical and atypical medications in an ethnically and phenotypically homogeneous sample.

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Treatment of Olfactory Hallucinations with Topiramate

To the Editors:

The authors report a case of olfactory hallucinations in a schizophrenic patient. The patient’s symptoms were described as intermittent smells of “dog feces,” “wet dog,” and/or “fungus,” lasting from “minutes” to “hours,” occurring once or twice daily for four years prior to presentation. These symptoms persisted despite antipsychotic treatment, but were treated to complete resolution with topiramate.

CASE REPORT

A 36-year-old man, with a 10-year history of psychotic disorder, presented to jail psychiatric inpatient services after accusing corrections officers of “throwing smells of feces” into his room. He had had a similar presentation with olfactory hallucinations. He reported multiple previous trials of antipsychotics. A short trial of valproic acid was discontinued because of transaminitis. His olfactory hallucinations did not respond to these medication trials. However, his thought process became more linear and organized, and the intensity of his delusional beliefs about the source of the smells decreased. An electroencephalogram (EEG) performed shortly after his first hospitalization revealed no epileptiform activity. However, there was no note of whether he had experienced hallucinations at the time of the EEG study.

On the current presentation, he reported that the smells that officers were “throwing at him” expanded into (his) mouth and cell. The sensations of the olfactory hallucinations were of “dog feces,” “fungus,” and/or “a wet dog.” They were intermittent, lasting minutes to hours, occurring once or twice a day, and accompanied by gustatory hallucinations of dog feces. The patient complained of abdominal pain (by which he may have meant nausea) after the hallucinations. He felt that all jail staff was persecuting him with these horrible smells. He threatened unidentified others he believed responsible for “spraying smells” into his cell. He was observed apparently attempting to rid himself of the sensations of smell and taste by washing his mouth frequently with soap and eating his toothpaste, which led to buccal erosions and oral pain.

He appeared moderately distressed, paced about his cell, and accused staff of “spraying smells.” His affect was anxious, full, and congruent. He quickly escalated to anger when discussing his olfactory hallucinations. His speech was rapid, although not pressured, and normal in volume and tone. His thought process was tangential. Mini-Mental State Examination score was 20 of 27, with deficits in attention and delayed recall. A neurological examination indicated abnormality of the olfactory system; when he was asked to identify smells with his eyes closed, he initially identified the smell of hand soap as “urine.” No automatisms, posturing, or confusion were observed around the periods when he reported experiencing hallucinations.

He was started on risperidone 1 mg BID and lithium carbonate 300 mg BID. His risperidone was soon increased to 2 mg BID. Although he continued to believe that his olfactory hallucinations were caused by unidentified others spraying smells into his room, he was willing to accept that there may be a “medical cause” for them and stopped making retaliatory threats. As such, despite his remaining olfactory hallucinations, he was discharged from the inpatient unit to the general jail population.

Two weeks later, he returned to the inpatient psychiatric service on an involuntary hold for grave disability after repeatedly pressing his cell’s emergency call button and complaining of “terrible smells.” On readmission, he repeated his delusion that an unidentified “they” continually sprayed his room with fecal and fungal smells. He blamed staff for “spraying smells” in his cell. He was paranoid and angry and refused medications. His speech was rapid and pressured; his thoughts were tangential; and he was intrusive and difficult to redirect. A repeat EEG showed no epileptiform or interictal activity. Of note, there was no record or whether he was experiencing olfactory hallucinations at the time of the EEG. Magnetic resonance imaging showed no mass or structural abnormalities.

He began taking topiramate 25 mg BID, which was soon titrated to 75 mg BID, along with risperidone 1 mg BID, which was increased to 2 mg BID. His symptoms improved remarkably over 5 days. He no longer voiced paranoid thoughts about staff or officers spraying smells on him. He reported that the smells had ceased. One month after discharge, topiramate was decreased to 50 mg BID, to decrease a side effect of gastrointestinal upset. Shortly after this decrease in dose, his olfactory hallucinations returned. He accepted an increase in dosage to topiramate 75 mg BID and then eventually to 125 mg BID. At the time of this writing, he is on topiramate 125 mg BID and is hallucination-free. He has been on risperidone 2 mg BID throughout the period of topiramate adjustment. He has also been free of paranoid delusions and other psychotic symptoms during this time.

DISCUSSION

Olfactory dysfunction, misinterpretation of odor, deficits in olfactory sensitivity threshold, and abnormalities in odor memory are common in schizophrenia. The prevalence of olfactory hallucinations has been reported between 11% and 36% of schizophrenic patients. Other neuropsychiatric disorders may present with olfactory hallucinations, including traumatic brain injury, cluster and migraine headaches, seizure disorders, central nervous system tumors, cerebral aneurysms, substance abuse, mood disorders, eating disorders, the olfactory reference syndrome (an excessive, irrational fear that one is emitting a foul or unpleasant odor), and iatrogenic conditions.

One old study suggests that olfactory hallucinations in schizophrenia are resistant to antipsychotic treatment. Furthermore, reportedly successful treatment options for idiopathic olfactory hallucinations include surgical extirpation of the olfactory epithelium and olfactory bulb ablation. Majumdar et al reported 2 cases of idiopathic olfactory hallucinations responsive to anticonvulsant therapy (sodium valproate and phenytoin). Kopala et al noted that schizophrenic subjects with olfactory hallucinations described unpleasant odors such as “stale cigarettes” or “feces.” Meats’ observed
that olfactory hallucinations as the primary complaint with secondary delusional interpretations may be a rare presentation of late onset paranoid schizophrenia. However, Meats\(^7\) also observed that, most commonly, olfactory hallucinations in schizophrenia were “subordinate” to other psychiatric symptoms.

It has been well established that olfactory dysfunctions of odor identification, odor detection threshold sensitivity, and odor memory are present in schizophrenia.\(^4\) However, it is not clear that olfactory hallucinations are necessarily related to this generalized olfactory dysfunction. In particular, 2 studies\(^5,6\) have demonstrated no correlation between the presence of olfactory hallucinations and olfactory dysfunction as identified the University of Pennsylvania Smell Identification Test.\(^8\) There are few studies that have implicated the medial temporal structures in the pathogenesis of olfactory dysfunction in schizophrenia.\(^4\) Deep brain stimulation studies on epileptic patients showed that olfactory hallucinations might be caused by left amygdala stimulation.\(^9\) Moreover, of 13 patients with olfactory epileptic auras, all showed epileptic foci in the mesial-temporal region.\(^10\)

Given no evidence of structural abnormality or epileptic focus and robust response to topiramate, we speculate, as did Majumdar et al,\(^5\) that there may be a focus of abnormal signal generation and reverberating circuits possibly in the mesial-temporal region. Evidence has been growing for the involvement of such reverberating circuits resulting in neuropsychiatric symptoms. For example, Llinas et al\(^11\) used magnetoencephalography to demonstrate abnormal low-frequency thalamocortical oscillatory activity in neuropsychiatric patients was recorded. Such persistent low-frequency thalamocortical dysrhythmia has been recorded in patients with schizophrenia.\(^12\) Moreover, the postulated inhibitory effect of \(\gamma\)-aminobutyric acid on these circuits may explain why topiramate, which enhances \(\gamma\)-aminobutyric acid receptor activity, was effective in our case.

A patient presenting to a psychiatrist with olfactory hallucinations is uncommon in clinical practice. Given the symptom’s correlation with structural abnormalities, a complete neurological evaluation (including EEG studies to rule out seizure disorder) should be performed in such a patient. Clinicians may try using an anticonvulsant such as topiramate in such a case, especially when olfactory hallucinations are refractory to otherwise therapeutic doses of antipsychotics.

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The Effects of Topiramate Adjunctive Treatment Added to Antidepressants in Patients with Resistant Obsessive-compulsive Disorder

To the Editors:

Obsessive-compulsive disorder (OCD) is a chronic disorder associated to substantial impact on the quality of life. Serotonin reuptake inhibitors (SRIs) are considered first-line treatments for OCD with response rates ranging from 42% to 53%.\(^7\) Many patients receive some benefit but remain symptomatic despite an adequate SRI trial. Little practical advice is available to clinicians on next-step treatment strategies for patients who have not responded to 2 or more trials of SRIs.

Hollander et al\(^1\) list behavioral therapy and a trial of clomipramine as the 2 options most often used in the treatment of refractory OCD. The combination of SSRIs with medications, such as risperidone, olanzapine, pindolol, buspirone, lithium, morphine, and thyroid hormones, have been reported.\(^2\) Efficacy has been found in double-blind studies using haloperidol, risperidone, quetiapine, and pindolol as augmentation agents in treatment-resistant OCD. Case reports of significant response to carbamazepine and sodium valproate have also been reported.\(^3\)

Topiramate is an anticonvulsant with a novel chemical structure. It has been used to treat bipolar disorder, binge-eating disorder, alcohol dependence, and impulse control disorders.\(^4\) Topiramate presents several mechanisms of action: enhances the activity of \(\gamma\)-aminobutyric acid at nonbenzodiazepine sites, blocks voltage-gated sodium channels, weakly

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inhibits carbonic anhydrase isoenzymes CAII and CAIV, and inhibits glutamate via alpha adenosine monophosphate/kainate.\(^5,6\)

Rosenberg et al\(^7\) by using single-voxel proton magnetic resonance spectroscopy reported normally high glutamatergic concentrations in the caudate nuclei of children with OCD. After selective SRI (SSRI) treatment, a decrease in OCD symptoms severity was associated with a reduction in caudate glutamatergic concentrations. Considering these results about an association between decreased caudate glutamatergic concentrations and a reduction in OCD symptoms as well as topiramate inhibitory effects on glutamate, we found of interest to investigate in this study the effects of adjunctive topiramate in treatment-resistant OCD.

Twelve consecutive subjects with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)–defined OCD for more than 3 years who had failed 2 or more adequate SRI trials were recruited. Topiramate therapy was added over 16 weeks. Patients were seen approximately every 2 weeks. Inclusion criteria included the following: male or female; aged 18 to 65 years old; meet DSM-IV criteria for OCD (by structured clinical interview [SCID]\(^8\)); informed consent given by patients; received an adequate trial of 14 or more weeks of open flexible dose treatment of an SRI (fluoxetine 80 mg/d, paroxetine 60 mg/d, fluvoxamine 300 mg/d, clomipramine 250 mg/d, sertraline 200 mg/d, citalopram 60 mg/d, or venlafaxine 300 mg/d); and have not responded or partially responded (Yale-Brown Obsessive-compulsive Scale [Y-BOCS] <30% of baseline score). Exclusion criteria were the following: any other primary Axis I psychiatric diagnosis; current DSM-IV eating disorder, body dysmorphic disorder, alcohol or substance abuse disorder, Axis II cluster B personality disorders (borderline or antisocial), history of bipolar disorder, schizophrenia, delirium, dementia or other cognitive disorders, initiation of psychotherapy within 4 months, seizure disorders, history of kidney stones, and Y-BOCS–baseline score of 16 or lower.

Topiramate was initially started at 25 mg/d. The dose was increased by 25 mg the first week, then increased by 50 mg increments for the following week, up to 100 mg/d at the end of week 3. The dose was titrated upward until a clinical response was achieved. At the end of week 5, the topiramate dose could be further increased by 50 mg/d each week up to a maximum dose of 400 mg/d at week 9, if intolerance occurred the dose was adjusted accordingly. All patients were rated by the treating clinician at 2 weeks intervals using the Y-BOCS\(^9\) and the Global Assessment of Functioning (GAF) Scale\(^10\) for measuring social functioning.

Subjects were permitted to continue taking concurrent benzodiazepines (n = 2) or antidepressant medications, provided that they have been on a stable dose of these medications for at least 8 weeks before entering the study and agreed not to change the dose of the concurrent medication over the course of the study.

Primary efficacy measurement was defined as the number of responders with Y-BOCS less than 30% of Y-BOCS–baseline score. For changes between baseline and follow-up assessments, Wilcoxon signed rank test was used (Statistical Package for Social Sciences, version 9.0; SPSS, Chicago, IL).

The sample included 7 men and 5 women who had a mean of 46.6 ± 7.7 years, a mean age of OCD diagnoses 30.3 ± 3.7. At baseline, the means of Y-BOCS and GAF scores were 28.3 ± 2.7 and 47.3 ± 3.4, respectively. Patients demographics, concurrent diagnoses, treatment history, and response are listed in Table 1. All patients completed the follow-up study. Ten patients were considered responders (83%). A significant change was found from baseline to end point in Y-BOCS (z = −3.063, \(P = 0.002\)) and GAF scores (z = −3.064, \(P = 0.002\)). There were no correlations between doses of topiramate and changes in Y-BOCS and GAF (\(f^2 = 0.087,\)

### TABLE 1. Clinical Characteristics of the Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Sex Diagnosis</th>
<th>Comorbid Diagnoses</th>
<th>Antidepressant (mg/d)</th>
<th>Topiramate Dose Added (mg/d)</th>
<th>Y-BOCS (Basal)</th>
<th>Y-BOCS (16 weeks)</th>
<th>GAF Basal</th>
<th>GAF (16 weeks)</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>50</td>
<td>28</td>
<td>None</td>
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<td>250</td>
<td>23</td>
<td>16</td>
<td>43</td>
<td>68</td>
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<td>2</td>
<td>M</td>
<td>47</td>
<td>32</td>
<td>PD</td>
<td>Clomipramine (250), clonazepam (4)</td>
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<td>25</td>
<td>12</td>
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<td>75</td>
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<td>M</td>
<td>45</td>
<td>30</td>
<td>SPh</td>
<td>Fluoxetine (80), diazepam (10)</td>
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<td>M</td>
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<td>8</td>
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<tr>
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</table>

Dys indicates dysthima; GAD, generalized anxiety disorder; MDD, major depressive disorder; PD, panic disorder; SPh, social phobia.
valproate and carbamazepine, have been result an effective strategy to treat that this drug was well tolerated and may of OCD. The results presented suggest difficulties (2/12), and paresthesia (2/12).

This is the first study in which topiramate has been used in the treatment of OCD. The results presented suggest that this drug was well tolerated and may result in OCD. Other anticonvulsants, valproate and carbamazepine, have been useful in the treatment of OCD associated to other psychiatric conditions.

A common model for addictive behaviors (alcohol dependence) and OCD has been suggested. In fact, obsessive-compulsive drinking scale is being used in studies on alcohol dependence. In a recent study, topiramate was better than placebo to decrease obsessive-compulsive drinking scale scores. Furthermore, topiramate was useful in the treatment of cocaine or alcohol dependence and in other disorders with compulsive behaviors, such as binge eating and compulsive gambling.

The precise neurochemical mechanism by which topiramate improved the efficacy of the treatment in OCD patients resistant to antidepressants remains to be elucidated. However, it is tempting to speculate that modifications in glutamatergic function may be responsible, at least in part, of the improved response of topiramate. Glutamatergic dysfunction was a common mechanism involved in both type of disorders, OCD and addictions. It has been suggested that efficacy of SSRIs and their actions in the treatment of OCD could be associated with glutamate neurotransmission. In addition, topiramate could decrease alcohol drinking by antagonizing glutamate receptors. In fact, nicotine withdrawal symptoms are reverted by administration of glutamate receptor antagonist. Therefore, it can be hypothesized that glutamatergic dysfunction could be involved on compulsive behaviors associated to OCD and on compulsive consumptions of addictive disorders. In both cases, topiramate may represent a useful pharmacological strategy. In OCD, topiramate improves the control of compulsive behaviors allowing patients to reduce obsessive thoughts, as behavioral therapies based on response prevention techniques.

In conclusion, the results of this study show that administration topiramate together to antidepressants significantly improved the symptoms of OCD patients resistant to antidepressant treatments. Main limitations of the study are related to low number of patients included and because the open design. However, further well-designed studies are needed to determine efficacy of this strategy.

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Much Improved Outcome With Gabapentin-divalproex Combination in Adults With Bipolar Disorders and Developmental Disabilities

To the Editors:

Many preliminary reports suggest that gabapentin (GP), the add-on antiseizure medication, improves mood stabilization. Because persons with mental retardation (MR) manifest more side effects of lithium, we studied GP as an alternative add-on mood stabilizer to divalproex (DVP; Abbott Pharmaceuticals).

Antiepileptic mood-stabilizing agents including DVP, may be more effective than lithium for acute and maintenance treatment of patients with mixed, chronic, or rapid-cycling bipolar disorders. Combination treatment of DVP and another mood stabilizer together with low-dose antipsychotic drug may be required to achieve adequate stabilization in resistant cases. Patients with MR are more likely to present with aggression and to experience chronic, mixed, or rapid cycling bipolar disorder responsive to combination mood stabilizers. Lithium treatment is commonly used for bipolar disorder; however, persons with MR often manifest severe problematic side effects and risks of lithium treatment.

A prominent side effect produced by lithium in this population is hand tremor, often marked and disabling. Tremor worsens when lithium is combined with DVP and antipsychotic drugs. Excessive drinking and enuresis are common. Lithium toxicity is serious and a potentially lethal risk which is greater in this population because of difficulties with self-monitoring of fluid intake and illness reporting. Other lithium side effects include cognitive slowing and blurred vision, which persons with MR may be unable to report. Glomerular damage and renal failure may result from chronic lithium treatment. Lithium may worsen seizure disorders, which are a common problem in this population. For these reasons, trial of an adjunctive antiseizure medication in place of lithium is warranted and may improve safety in this population.

Gabapentin, which was marketed with a therapeutic range of 100 to 1800 mg/d, is available in liquid form and has a better safety profile than lithium. Although GP is renally excreted like lithium, it has a higher therapeutic index. Thus, in the absence of renal failure, toxicity is less likely to be associated with therapeutic doses. It does not bind significantly to plasma proteins nor does it interact with drug-metabolizing enzymes in the liver. This reasoning led to the present trial of the newer antiseizure medication GP (Neurontin) in place of lithium. Side effects of lethargy, sedation, ataxia, and dizziness occur in 10% of patients receiving GP and are dose related. Nausea, diarrhea, increased appetite and weight gain, headache, tremor, and nystagmus are less-frequent side effects which usually resolve after a few weeks of treatment.

Clinical chart data were reviewed of 30 patients with MR diagnosed with bipolar mood disorder or schizoaffective disorder, bipolar type, who received GP as add-on treatment to DVP. All diagnoses were made by the author and the psychiatry resident in our University MR/Autism Psychiatric Adult Outpatient specialty clinic using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. Treatment success was defined as Clinical Global Impressions (CGI)—Severity of 4 (moderate problem) or less and CGI-Improvement of at least much improved. In one subgroup (n = 13), we examined treatment outcome after GP addition to DVP treatment for partial DVP responders. In another subgroup of patients (n = 17) already stabilized on the combination of lithium and DVP, we examined efficacy and safety of adding GP and gradually tapering off the lithium. Concomitant low-dose antipsychotic drug treatment was not an exclusion criterion, provided this was not begun in the month prior, and the dosage was held constant during the GP trial.

Written informed consent for a clinical trial of GP treatment was obtained from the patient or guardian before starting the medication. In each case, GP was gradually introduced, starting with 100 mg at night for 3 to 7 days, then 100 mg BID for 3 to 7 days; then 100 mg TID to continue. The slower weekly dosage increase was used for patients with compromised motor function or gait disturbance to avoid possible sedation, clumsiness, and falling. In most cases, the dose was then again gradually increased as above, stepwise to 300 mg TID as a minimum therapeutic dose (see Table 1). A CGI was completed at baseline and thereafter at each visit by the treating clinician (J.H.).

Lithium taper was attempted extremely gradually in those individuals in the subgroup of 17 patients receiving lithium-DVP combination, by 150 to 300 mg every 3 to 4 months. Gabapentin dose was increased further if a recurrence of clinically mild or moderate symptoms of mood disorder or aggression occurred. Lithium was again increased in those patients who developed significant relapse in mood or aggressive symptoms, or reintroduced for those patients in whom it had been discontinued. These were recorded as failures of GP replacement of lithium.

Of the 30 adult patients in this series, 13 received GP as add-on to DVP. Twelve (92.3%) of the 13 were rated as moderate problem or less and as much improved at 3 months and 1 year (see Table 1). At 5.3 years mean duration of follow-up (range, 4–8 years), 9 (84.6%) of the 11 continuing to follow up in our clinic remained a moderate problem or less, and much improved on CGI. Two patients (numbers 9 and 10) were lost to follow-up, one (patient 4) had ongoing partial seizures, mood lability, and bipolar symptoms, and one (patient 8) had...
ongoing depressive cycles with psychomotor retardation now showing preliminary response to lamotrigine combined with DVP and an antipsychotic. The median GP dose in this subgroup was 1200 mg daily (range, 600–2100 mg daily). Two patients in group 1 had partially controlled epilepsy: patient 4, as mentioned above, and patient 8. Three other patients had a remote history of seizures.

In the other subgroup of 17 patients, replacement of lithium by GP in combination with DVP was successfully achieved in 9 patients (52.9%), all of whom remained a moderate problem (CGI-S of 4 or less) and much improved and had significantly reduced tremor at 3 months and also at 1 year (see Table 1). At 5.1 years mean duration (range, 2.5–7 years), all 8 patients continuing on the GP-DVP combination remained much improved. One patient (no. 28) had been started by his general practitioner on anti-Parkinson medication for the tremor, despite our communications that it was more likely associated with lithium together with DVP and antipsychotic drug. The tremor resolved after lithium was discontinued. Overall, 8 patients (47.1%) failed conversion from lithium to GP because of relapsing bipolar symptoms. Three of these relapses occurred during lithium taper, in one case with associated long-standing compliance issues that had already required repeated hospitalizations. Another 3 patients relapsed after several months off lithium, requiring lithium to be reinstituted. Another subject who relapsed during lithium taper had associated renal failure attributed to the lithium. To accommodate for this, her GP dose was relatively low at 400 mg/d. However, her blood level was in the therapeutic range for seizures at 8.1 μg/mL. Thus, 8 (47.1%) of the 17 patients were unable to maintain improvement off lithium on GP and DVP, whereas success was achieved in 9 cases.

### TABLE 1. Outcome for GP Addition to DVP (Patients 1–13) and GP Replacement of Lithium in Combination With DVP (Patients 14–30)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Starting Age</th>
<th>Sex</th>
<th>GP Dose, mg (Level)</th>
<th>DVP Dose, mg (Level)</th>
<th>Antipsychotic Dose, mg</th>
<th>CGI-Severity</th>
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<tr>
<td></td>
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<td>GP Dose, mg (Level)</td>
<td>DVP Dose, mg (Level)</td>
<td>Antipsychotic Dose, mg</td>
<td>Baseline</td>
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<td>1000 (72)</td>
<td>Risperidone 2</td>
<td>3</td>
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<td>2</td>
<td>35</td>
<td>M</td>
<td>1800 (4.2)</td>
<td>1750 (77.0)</td>
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<tr>
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<td>36</td>
<td>M</td>
<td>600 (8.5)</td>
<td>1000 (58)</td>
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<td>27</td>
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<td>1500 (95)</td>
<td>—</td>
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<td>45</td>
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<tr>
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<td>1250 (98)</td>
<td>—</td>
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<td>13</td>
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<td>F</td>
<td>2500 (3.9)</td>
<td>1250 (64.8)</td>
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<td>1750 (24.1)</td>
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<tr>
<td>24</td>
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<td>1000 (52.7)</td>
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<td>900 (1.8)</td>
<td>2000 (65.5)</td>
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<td>4</td>
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<tr>
<td>26</td>
<td>40</td>
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<td>27</td>
<td>37</td>
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<td>900 (NA)</td>
<td>CBZ 400 (8.9)</td>
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<tr>
<td>28</td>
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<td>1000 (72.8)</td>
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<tr>
<td>29</td>
<td>46</td>
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<td>CBZ 500,300 (9.5)</td>
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<tr>
<td>30</td>
<td>46</td>
<td>F</td>
<td>400 (8.1)</td>
<td>1500 (39)</td>
<td>Risperidone 2, thioridazine 150</td>
<td>4</td>
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</table>

GP levels are given in mcg/mL; DVP levels, mg/mL; CBZ levels, mcg/mL; Lithium levels, meq/L. CBZ indicates carbamazepine; LTF, lost to follow-up; NA, not available.
Combination Therapy of Lamotrigine and Escitalopram May Cause Myoclonus

To the Editors:

The term myoclonus refers to brief, involuntary jerking of a muscle or a group of muscles. It is a symptom of various diseases including neurodegenerative and systemic metabolic disorders. In addition, myoclonus has been described as a side effect of several drugs; it is well established that it can be caused by levodopa, cyclic antidepressants, and bismuth salts, while there exist only very few studies reporting that selective serotonin receptor inhibitors (SSRIs) or newer anticonvulsants like lamotrigine (LTG) can induce myoclonus as well.¹

Furthermore, the induction of myoclonus has been linked with calcium channel-blocking drugs like verapamil.² It is known that voltage-gated calcium channels can be inhibited by LTG. Janszky et al³ reported that 2 patients with epilepsy experienced disabling myoclonic jerks during LTG treatment.

Interestingly, also SSRIs are able to inhibit voltage-gated ion channels.⁴ The SSRi citalopram (CT) is metabolized mainly by cytochrome P450 (CYP)2D6 enzyme. Inhibition of CYP2D6 results in increasing plasma levels of that antidepressant. Spigset et al⁵ reported on myoclonus associated with CT treatment in patients treated with an additional CYP2D6-inhibiting drug. CT is a racemic mixture of R-CT and its pharmacologically active S-enantiomer escitalopram (S-CT). S-CT was raised to 20 mg/d, that patient noticed the onset of myoclonus (LTG, 6.5, 7.1, and 6.1 mg/L [reference value, 1–13 mg/L]; S-CT, 66, 76, and 71 ng/mL [in the reference frame]). Myoclonus did not stop during the following months under equal medical treatment conditions. Analysis of CYP2D6, CYP19, and CYP3A4 revealed normal enzymatic activity, indicating the patient to be a normal metabolizer.

A 28-year-old woman, affected by epilepsy, was admitted to our neurological inpatient unit because of a seizure during treatment with LTG (200 mg/d; serum level, 5.5 mg/L). This was the fifth seizure in the last 5 years. Hence, LTG dosage was raised to 300 mg/d. Until now, 9 months later, no seizure occurred again. In addition, this patient suffers from generalized anxiety disorder. Therefore, we started psychopharmacological treatment with S-CT (starting dosage, 10 mg/d). Two weeks later, after dosage of S-CT was raised to 20 mg/d, no patient observed onset of myoclonus during nighttime and daytime. At that timepoint, the serum LTG level was 7.1 mg/L and the serum S-CT level was 40 ng/mL. The frequency of the myoclonus did not alter for 6 months but stopped 2 weeks after

REFERENCES


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Dr Hellings is a consultant to Abbott Pharmaceuticals. Supported by Abbott unrestricted $5000 grant; NIMH grant number MH01516-K08; and NICHD grant numbers HD02528.

discontinuation of the treatment with S-CT. We could not determine any changes in LTG serum levels after discontinuation of S-CT treatment.

These cases suggest that LTG enhances the onset of myoclonus if combined with S-CT. Myoclonus, a symptom of the serotonin syndrome, is a known side effect of treatment with SSRIs like S-CT. Interestingly, LTG is also able to induce myoclonus—provided that high LTG serum levels are reached. Although the main property of LTG is the inhibition of glutamate release, thereby combating epilepsy and myoclonus, LTG is apparently able to amplify the risk of developing myoclonus alone or in combination therapy with an SSRI. Chronic administration of LTG downregulates cortical 5-HT1A receptor density thereby sensitizing the serotonergic system for incidence of serotonin syndrome caused by substances increasing the amount of serotonin in the synaptic cleft. Erfurth et al. showed female genital disorder as adverse symptom of LTG treatment and suggest this to be a serotonergic side effect induced by high doses of SSRIs. Therefore, we consider LTG and S-CT to have additive or even synergistic effects on the 5-HT1A receptor and its linked enzyme system (adenyl cyclase).

Another conceivable hypothesis is a possible additive blocking effect of LTG and S-CT on voltage-gated calcium channels. As already mentioned, LTG is known to block the N-type calcium channel. Hahn et al. showed an inhibition of voltage-activated calcium channels by the SSRI fluoxetine. Vadlamudi et al. reported on multifocal myoclonus caused by an intentional overdose of the calcium channel blocker verapamil. Vadlamudi et al also describe cases with other calcium channel blockers, for example, nifedipine.

Taken these 2 hypotheses into account, combination therapy with LTG and SSRIs has the capability to trigger the incidence of myoclonus.

Myoclonus is a known side effect of valproic acid, carbamazepine, and tricyclic antidepressants, whereas LTG and SSRIs so far were not listed as substances inducing myoclonus. Interactions of metabolic enzymes of LTG and S-CT, as hypothesized in a previous study regarding LTG and sertraline are improbable, because LTG is primarily metabolized through glucuronidation. Hence, impaired enzyme activity caused by a genetic “poor metabolizer” polymorphism is unlikely to have large effects on net metabolic clearance of any of the substances.

Clinicians treating their patients with a combination therapy of an SSRI and LTG should look out carefully for symptoms of the serotonin syndrome. We propose that LTG and SSRIs share at least a few serotonin receptor subtypes. This particular variation of LTG may also account for its robust activity against depression, whereas other anticonvulsants like carbamazepine and valproate seem to exert stronger antimanic effects.

For this study, written informed consent and human subjects research committee approval were obtained.

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REFERENCES

Levetiracetam for the Treatment of Alcohol Withdrawal Syndrome: An Open-label Pilot Trial

To the Editors:

Alcohol withdrawal syndrome (AWS) is a serious complication of alcohol dependence and often requires an intensive medical treatment and hospital admission. The most recommended treatment regimen for AWS are benzodiazepines (BDZs). As an alternative, antiepileptic drugs (AEDs) (eg, carbamazepine and valproate) have been shown to be efficacious in the treatment of AWS in several controlled trials. However, BDZs and most of the AEDs are limited by side effects, especially liver toxicity. In contrast, the AED levetiracetam, a pyrrolidone derivative, has a favorable safety profile, shown in placebo-controlled trials in epilepsy. Recently, levetiracetam has been shown to reduce AWS in alcohol-dependent mice, suggesting that levetiracetam may...
consent was obtained. We therefore initiated an open-label pilot trial to evaluate the efficacy and safety of levetiracetam for the treatment of AWS in patients with severe alcoholism.

Overall, 15 patients (3 women and 12 men) of central European origin with a mean age of 40.5 years (SD, 10.2 years; range, 22–53 years) who were voluntarily seeking treatment for alcohol detoxification were included in this trial. All patients fulfilled Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for alcohol dependence and had an imminent moderate to severe AWS with the need of medical treatment. Three of the 15 patients had an untreated comorbid major depression. Exclusion criteria were alcohol withdrawal delirium, illicit drug use in the 30 days before admission, last alcohol beverage intake more than 72 hours before admission, current use of anticonvulsive medication or BDZs, pregnancy, and serious medical conditions. The trial was approved by the local ethics committee. After a complete description of the study to the subjects, fully informed written consent was obtained.

The severity of AWS was assessed using the AWS Scale,6 a validated reliable measure of mental and somatic symptoms of the current severity of alcohol withdrawal consisting of 10 items (blood pressure, pulse rate, breathing rate, sweating, tremor, agitation, contact, orientation, hallucinations, and anxiety), scored from 0 (no withdrawal) to 32 (maximum withdrawal severity). The AWS Scale was administered at least 4 times a day during the study period. Levetiracetam was given in a fixed-schedule regimen (Table 1) in 500-mg tablets during 6 days between 500 and 2000 mg/d. Treatment was started with 1000 mg/d, which was given to the patients immediately after admission, independently from blood alcohol concentration. Clonidine 75 µg/d up to a maximum of 400 µg/d was given in case of hypertension. Diazepam 5 mg/d up to a maximum of 30 mg/d was administered as needed according to persistent withdrawal symptoms or moderate to severe insomnia. Statistical analyses were performed using t tests for dependent samples. The global α level was 0.05, Bonferroni correction was applied for multiple testing (n = 3), and the P level was adjusted to less than 0.016.

All patients successfully completed the alcohol withdrawal treatment. Eight (53.3%) of the 15 patients could be treated with levetiracetam as monotherapy. The mean of maximal AWS Scale scores on day 1 was 6.6 (SD, 2.2; range, 2–9). The mean scores of the AWS Scale decreased significantly from 4.6 (SD, 1.7) on day 1 to 1.9 (SD, 1.5) on day 3 to 0.5 (SD, 0.7) on day 7 (day 1 vs 3: t = 4.84, P < 0.001; day 1 vs 7: t = 9.66, P < .001). Within 3 days, most of the patients recovered from AWS. Seven patients (46.7%) received an add-on medication with diazepam (n = 2), clonidine (n = 3), or a combination of both (n = 2). The mean diazepam dose for those patients was 3.8 mg/d (SD, 1.4 mg/d; range, 1.4–10.8 mg/d) and overall 26.3 mg in 7 days (SD, 32.5 mg; range, 10–75 mg). The mean clonidine dose was 10.7 µg (SD, 49.3 µg; range, 10.7–117.9 µg) per day and overall 345.0 µg in 7 days (SD, 293.4 µg; range, 75–825 µg). Whereas 3 patients received diazepam 5 to 10 mg/d as single dose in the evening because of insomnia, only 1 patient received diazepam up to 20 mg/d because of ongoing moderate withdrawal symptoms. Four of the 15 patients complained about adverse events such as mild sedation (n = 3) or mild pruritus (n = 1), which were judged as possibly related to treatment with levetiracetam. None of these symptoms caused permanent or transient discontinuation of treatment. No major complications, such as seizures or delirium, could be observed.

Overall, treatment with levetiracetam resulted in a rapid clinical improvement of AWS in all patients; two thirds of the patients recovered from AWS within 3 days. In all of the patients, a positive outcome and a completion of levetiracetam treatment were achieved. No severe adverse events or complications according to AWS occurred. Only one patient had to be treated with additional diazepam because of withdrawal symptoms, whereas patients in other alcohol detoxification trials received daily diazepam dosages between 10 and 90 mg during the first 4 days.7 One major requirement for the treatment of AWS is an alternative to BDZ medication for patients with organic risk factors. The use of BDZs in AWS is based on their rapid sedation, anxiolytic effects, and antiepileptic properties, but they may cause the risk of abuse, intoxication with respiratory insufficiency, and cognitive impairment.8 Although BDZs and some AEDs (eg, carbamazepine and valproate) are relatively contraindicated in patients with liver diseases,9,10 as well as advantageous pharmacokinetics and no risk of drug interaction.4 Moreover, levetiracetam seems to have only a limited risk of intoxication or respiratory insufficiency in combination with alcohol due to its lack of GABAergic properties. However, the mechanism by which levetiracetam exerts its therapeutic effects in AWS is still unclear. Levetiracetam reduc9,11 as well as alcohol withdrawal syndrome5 in mice and was shown to have antikindling effects.12 Kindling is a model for understanding AWS: repeated episodes of alcohol withdrawal may kindle over time, increasing neuronal excitability, leading to progressively severe alcohol withdrawal including delirium and seizures.13 Due to its sedative effects4 similar to BDZs, levetiracetam may also decrease irritability and agitation in the first days of AWS. Levetiracetam does not appear to have significant activity against other drug targets of AEDs;4 moreover, there was no indication of direct effects on GABAergic mechanisms.14 Levetiracetam reduces currents through high-voltage–activated calcium channels, interacts with a unique binding site,15 and has high affinity to the SV2A protein16 that is involved in synaptic vesicle function and calcium-dependent regulation of neurotransmitter release during repetitive stimulation.17 Thus, levetiracetam might reduce excessive neuronal activity and thereby seizures and may also exert protective effects regarding the kindling effect of AWS.17

The results of this open-label pilot trial are preliminary and have to be
interpreted with caution because of the small number of patients and the lack of a control group, so further controlled trials with larger samples are needed. Nevertheless, these preliminary data provide evidence that levetiracetam is safe and efficacious in the treatment of acute AWS. The use of modern AEDs not affecting the liver such as levetiracetam may be an important strategy for the treatment of AWS in the future.

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REFERENCES

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