

# Letters to the Editor

## Divalproex Sodium for Alcohol Withdrawal and Relapse Prevention: A Case Report

**Sir:** The anticonvulsant mood stabilizers have emerged as useful agents in the treatment of a wide range of psychiatric disorders.<sup>1</sup> My colleagues and I have had good results using divalproex sodium for treatment of substance use disorders, especially for acute and protracted sedative-hypnotic withdrawal. The following case illustrates the efficacy of divalproex in a patient with a history of severe alcohol dependence without comorbid psychopathology.

**Case report.** Mr. A, a 51-year-old man with a 30-year history of heavy drinking, was admitted to our inpatient unit for alcohol detoxification. He reported an average daily consumption of 24 drink equivalents per day, including morning drinking to suppress autonomic withdrawal signs. Despite drinking during breaks and at lunch, Mr. A was able to maintain his job as a welder for a large manufacturing company. His motivation for seeking treatment stemmed from concerns about his physical health and subtle cognitive deficits, and pressure from his wife. He presented with no other diagnosable psychiatric conditions or history thereof.

At admission, Mr. A was administered a battery of alcohol screening instruments, scoring 26 on the Alcohol Dependency Scale<sup>2</sup> (ADS; range, 1–47) and clearly meeting all 7 DSM-IV diagnostic criteria for alcohol dependency syndrome. Results of baseline laboratory assessments included a mean corpuscular volume (MCV) of 112 and elevated liver function tests ( $\gamma$ -glutamyl transferase [GGT] level = 298 IU/L, alkaline phosphatase level = 128 IU/L, aspartate aminotransferase [AST] level = 49 IU/L) indicative of chronic alcoholism. Physical examination revealed no acute medical conditions or other complications of alcoholism.

Our treatment facility ordinarily utilizes a symptom-triggered benzodiazepine detoxification protocol, and Mr. A was monitored for alcohol withdrawal via the Clinical Institute Withdrawal Assessment-Alcohol revised (CIWA-Ar)<sup>3</sup> every 2 to 4 hours. The CIWA-Ar is a standardized assessment scale (range, 0–56) that measures objective alcohol withdrawal symptomatology. Eight hours after admission, his score elevated from a baseline rating of 7 to 16, and after providing informed consent (information outlined risks, benefits, and potential side effects of this experimental treatment protocol), he agreed to divalproex detoxification rather than the standard benzodiazepine detoxification. He was given a loading dose of divalproex, 750 mg (based on 20 mg/kg body weight), and 6 hours later was given the second half of his loading dose (750 mg). Mr. A's CIWA-Ar score declined during the 12 hours after initiation of divalproex and remained lower than 6 for the rest of his hospitalization, and he suffered no residual withdrawal symptoms. His blood divalproex level at discharge (day 4) was 83 mg/mL, and he was maintained on a daily dose of 750 mg b.i.d. for 6 weeks.

Mr. A participated in 5 days of an intensive outpatient day program after discharge and then in once-weekly evening

group therapy sessions thereafter that focused on relapse prevention training. He was seen at 2-week and 6-week follow-up sessions to check medication compliance, side effects, and drinking measures. He maintained complete abstinence during this 6-week follow-up assessment phase and reported no medication side effects. Notably, Mr. A reported no craving, mood lability, irritability, or insomnia, which he had typically experienced during unsuccessful efforts to curtail his drinking in the past. At 6-week follow-up, his laboratory results had also improved (MCV = 106, GGT level = 111 IU/L, alkaline phosphatase level = 64 IU/L, AST level = 23 IU/L). His blood divalproex level was 38 mg/mL (20 hours after last dose). Mr. A felt secure in his ability to maintain his sobriety, and divalproex was subsequently tapered and discontinued. He remains abstinent.

This case illustrates the potential utility of divalproex sodium for both management of acute alcohol withdrawal and relapse prevention. Certain anticonvulsants (divalproex sodium, carbamazepine) are commonly used for benzodiazepine detoxification, and given their GABAergic and anticonvulsant effects, it is reasonable to surmise that they may also effectively mitigate alcohol withdrawal symptomatology.<sup>4,5</sup> Furthermore, divalproex may offer significant advantages over benzodiazepines for outpatient detoxification since it does not react synergistically with alcohol, has no abuse potential, and, in contrast to other anticonvulsants, can be administered via oral loading dosing to ensure a rapid onset of effect.<sup>6,7</sup>

Although the use of a potentially hepatotoxic drug in individuals with preexisting liver disease requires careful consideration of risks versus benefits, it is certainly not without precedent in alcoholic populations. In fact, the 2 U.S. Food and Drug Administration-approved medications currently available for the treatment of alcoholism, naltrexone and disulfiram, are also potentially hepatotoxic, yet most successfully treated patients display lower transaminase levels posttreatment than at baseline, presumably because they are drinking less.<sup>8,9</sup>

Many alcohol-dependent individuals also have underlying affective illnesses that remain undiagnosed and untreated; mood stabilizers may be useful for these individuals. Additionally, as in the present case, many alcoholics feel subsyndromally “keyed up and on edge,” irritable, and cannot sleep when they attempt to quit drinking and are thus unsuccessful and relapse. These individuals may also benefit from the anticonvulsant mood stabilizers.

Pharmacologic interventions for the treatment of alcoholism are currently areas of research priority for the National Institute on Alcohol Abuse and Alcoholism, and clearly the utility of anticonvulsants such as divalproex sodium warrants further study. We are currently evaluating a larger case series comparing short-term (detoxification only) and long-term divalproex maintenance treatment groups versus a control group detoxified using a standard benzodiazepine.

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**Lance P. Longo, M.D.**  
 Sinai Samaritan Medical Center  
 Milwaukee, Wisconsin

### The Effectiveness of Combining Lithium With Olanzapine in the Treatment of Resistant Schizophrenia

**Sir:** The Expert Consensus panel<sup>1</sup> agrees that adding lithium to conventional antipsychotics for treating resistant schizophrenia can be a second-line alternative, although a recent trial found no response with lithium augmentation.<sup>2</sup> This combination can improve both psychotic and affective symptoms.<sup>3</sup> Olanzapine is a new, atypical antipsychotic medication that seems effective and safe in the treatment of schizophrenia.<sup>4</sup> Two open-label clinical trials<sup>5,6</sup> also suggest good results with olanzapine in individuals with resistant schizophrenia. Nevertheless, 1 double-blind comparison trial<sup>7</sup> obtained contrasting results in terms of effectiveness. We present our experience with 5 treatment-resistant schizophrenic patients (DSM-IV criteria<sup>8</sup>) who did not respond to olanzapine as monotherapy, but did exhibit improvements when lithium was added to the treatment.

**Case report.** The 5 patients were men, with an average age of 36 years, who were clinically diagnosed with paranoid schizophrenia, except 1 who had the residual type of schizophrenia. Patients had been diagnosed with the disorder for a mean of 16 years (range, 4-31 years), while the mean number of days in hospital was 407. The mean hospital admission stay during which this treatment was prescribed was 42 days. All patients had received the typical antipsychotic haloperidol. Two patients had also been treated with chlorpromazine, while 2 others had been treated with thioridazine. Four had received depot treatment with fluphenazine decanoate. All 5 had received clozapine treatment for a minimum of 2 months (dose range, 300-900 mg/day). Three had also received electroconvulsive therapy (8, 19, and 6 applications, respectively) owing to lack of response.

After these therapeutic strategies, olanzapine monotherapy was carried out. Mean  $\pm$  SD dose of olanzapine was  $27 \pm 4$  mg/day. However, each patient received olanzapine during a different time program: the shortest span was 1 month, while

the longest was 24 months. In an effort to cope with the poor therapeutic response achieved, lithium carbonate was added to olanzapine (dosage adjusted according to the therapeutic plasma range of 0.5-1.3 mEq/L). The mean lithium dose was 960 mg/day. None of the patients had received previous treatment with lithium.

The response was similar in all 5 patients: an initial improvement was observed between the seventh and tenth day. Specifically, behavioral symptoms and anxiety were reduced, social relationships improved, and although thought disorders persisted, patients could cope with them. This improvement, although partial, allowed patients to be discharged from the hospital.

After 8 months of treatment with this combination, 1 patient was hospitalized in the Internal Medicine Service. After this patient was diagnosed with idiopathic liver cirrhosis, this Service recommended the withdrawal of lithium. Seventy days later, this patient suffered a psychiatric relapse. After consultation with the Internal Medicine Service, lithium was again prescribed with good clinical response. No posttreatment elevation of liver enzymes was found. This was the only possible secondary effect observed when this combination was prescribed, although any link with lithium is extremely unlikely.

Currently, no systematic and controlled studies have evaluated the effectiveness and safety of the combination of lithium and olanzapine in the treatment of schizophrenia. One study using healthy volunteers found no secondary effects with this combination.<sup>9</sup> Combining lithium and olanzapine in the treatment of nonresponding schizophrenia could, in some cases, improve the therapeutic response without increasing secondary effects. However, larger sample groups and controlled trials are necessary to test this hypothesis.

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**Joaquín C. Martín, M.D.**  
**Ginés Palenciano, M.D.**  
**Rocío Pérez, M.D.**

Hospital Universitario de Valme  
 Seville, Spain

### Treatment of Primary Cranial Dystonia (Meige's Syndrome) With Clozapine

**Sir:** Primary dystonia is the most common form of dystonia, a difficult disorder to treat.<sup>1-3</sup> Although the effect of clozapine on *tardive* dystonia, a subtype of tardive dyskinesia and a serious side effect of neuroleptic drug treatment, has been reported in several case studies,<sup>4-8</sup> there are no reports to our knowledge of improvement of primary dystonia resulting from clozapine treatment. We report on a patient with severe and persistent primary cranial dystonia (Meige's syndrome), which successfully responded to clozapine.

**Case report.** Ms. A, a 56-year-old married woman, has been suffering for 14 years from blepharospasm and oromandibular dystonia that had resulted from by a transient torticollis of short duration. Before the appearance of dystonic symptoms, she had never been treated with neuroleptics, antidepressants, or other drugs known to cause dystonia. Also, no organic causes could be found. About 5 years before the onset of dystonia, Ms. A slowly developed slight symptoms of depression, which did not require psychiatric treatment. Thirteen years ago, she experienced a distinct deterioration that included insomnia, anhedonia, 3 suicide attempts, sudden drop in work performance, loss of interest and initiative, social retreat, and transient bizarre notions, which subsequently led to 3 admissions to our clinic and a diagnosis of conversional neurosis with facial tics and depression. To attenuate the cranial dystonia, a variety of medications have been tried during the last 13 years, including trihexyphenidyl, tetrabenazine, and benzodiazepines, each with little or no effect. For treatment of the blepharospasm, Ms. A receives periorbital injections of botulinum toxin every 3 months (for 6 years) with good effect.

During a recent (fourth) stay in our clinic (1998), we assumed a diagnosis of psychotic disorder not otherwise specified (according to DSM-IV code 298.9) and suspected schizophrenia simplex (according to ICD-10 code F 20.6). She then began treatment with clozapine, 50 mg/day (steady-state blood clozapine level = 81 ng/mL). Five days later, the oromandibular dystonia vanished completely. An Abnormal Involuntary Movement Scale (AIMS) examination prior to the beginning of clozapine treatment resulted in a total score of 16, which decreased to 1 after 5 days of clozapine treatment. To exclude other causes of improvement, we stopped clozapine after 2 weeks, at which time her AIMS score was 1. After 3 days, the oromandibular dystonia began to redevelop (AIMS score = 12). She restarted clozapine treatment, which again improved the oromandibular dystonia within 5 days (AIMS score = 4). By this time, the blepharospasm had begun to reappear as the effect of botulinum toxin was fading, indicating that clozapine had less influence on the blepharospasm. One year later, Ms. A came to our clinic for a checkup. The marked improvement of the dystonic symptoms has continued (AIMS score = 6). She now receives 100 mg/day of clozapine (blood clozapine level = 138 ng/mL).

Our observations indicate that clozapine may have a beneficial influence on primary cranial dystonia. The improvement was quite fast, as was shown in case reports of tardive dystonia.<sup>6,9</sup> Astonishingly, the required mean daily dosage of clozapine was much lower in our patient (50–100 mg) than in the case studies of tardive dystonia (200–550 mg).<sup>4-8</sup> The higher dosages could be explained by the fact that antipsychotic treatment was also required. Any possible positive effect of clozapine on the blepharospasm (as described in case reports of

tardive dystonia<sup>4,9</sup>) was difficult to assess because of the regular periorbital botulinum toxin injections, but appeared to be less pronounced. The blepharospasm perhaps could have been alleviated further by a higher dosage of clozapine, which Ms. A could not tolerate because of tiredness and weight gain. As was shown here, primary dystonia is often found to be associated with psychiatric problems.<sup>10-12</sup> To date, clozapine has not been used to treat primary dystonia probably because of the rare, but serious, side effect of agranulocytosis. Our case report shows that clozapine may lead to a significant reduction of primary dystonic symptoms without the common extrapyramidal side effects of the classic neuroleptics.

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Angelika Sieche, M.D.  
Henner Giedke, M.D.  
University of Tübingen  
Tübingen, Germany

### Severe Lithium Toxicity Induced by Combined Levofloxacin Administration

**Sir:** Several cases have been reported of lithium neurotoxicity when antibiotics are added to lithium therapy. Spectinomycin,<sup>1</sup> metronidazole,<sup>2</sup> and tetracyclines<sup>3,4</sup> have been reported to increase serum lithium concentrations in the above-mentioned cases. Here we report a first case of severe lithium neurotoxicity induced by possible interaction between lithium and levofloxacin, a fluoroquinolone.

**Case report.** Mr. A, a 56-year-old man with mild mental retardation, had been treated for DSM-IV bipolar I disorder for 5 years. His affective symptoms had been well maintained on a regimen of lithium carbonate, 1200 mg/day, and chlorproma-

zine, 50 mg/day. However, he thought that his good condition would continue without these medications and stopped taking the drugs. Three months after stopping medication, Mr. A was admitted to the hospital for developing manic symptoms. His previous drug regimen was restarted. His manic symptoms improved rapidly, and his illness was well controlled for the following 5 months. Mean  $\pm$  SD serum lithium and creatinine levels during the past 5 years were  $0.92 \pm 0.12$  mEq/L and  $0.91 \pm 0.19$  mg/dL, respectively.

In February 1999, when he was still in the hospital and was being treated with lithium carbonate monotherapy, 1200 mg/day, Mr. A developed bronchitis and was prescribed levofloxacin, 300 mg/day. Two days later, he developed gait ataxia, dysarthria, coarse tremor, dizziness, frequent vomiting, falling with difficulty rising, and progressive confusion. The character and timing of Mr. A's symptoms suggested a possible drug interaction between lithium and levofloxacin, leading to discontinuation of these drugs. The next morning, about 24 hours after administration of the last dose of lithium carbonate (400 mg), Mr. A's blood sample was drawn, revealing a lithium concentration of 2.53 mEq/L, which was more than twice his usual level. His plasma creatinine level had increased to 1.6 mg/dL, and creatinine clearance measured by using standard 24-hour urine collection was 56 mL/min at that time (normal range, 70–130 mL/min). There was no laboratory evidence of electrolyte disturbance or liver dysfunction. Electrocardiogram and computed tomographic scan of the head showed no abnormality.

Four days after stopping lithium and levofloxacin, the disturbing neurologic symptoms disappeared completely, with decrease in serum lithium level to 1.12 mEq/L and creatinine level to 1.0 mg/dL. Creatinine clearance increased to 105 mL/min at that time.

Renal disturbance is a common cause of lithium toxicity because lithium is removed from the body exclusively via renal excretion. Dehydration and electrolyte disturbance are other common causes of lithium toxicity, and patients with polyuria, which is one of the major side effects of lithium therapy, have also been reported to be at increased risk of lithium intoxication because of excessive loss of renal fluid.<sup>5</sup> However, no symptoms or examination results indicated such conditions in our patient. Acute lithium intoxication in our patient, therefore, is attributed to renal impairment induced by combined use of lithium and levofloxacin.

Reaching a blood lithium level of 2.53 mEq/L after only 3 days on treatment with the antibiotic might be unusual if the prior lithium and creatinine values were unchanged on or about the day he was prescribed levofloxacin. Unfortunately, a blood sample was not obtained at that time, so we could not ascertain the levels of lithium and creatinine just before the administration of levofloxacin. However, the last blood sample prior to the lithium intoxication was drawn about 2 weeks before prescribing levofloxacin. The data from this blood sample showed the lithium level to be 0.89 mEq/L and the creatinine level to be 1.0 mg/dL, which are within the normal range. No clinical symptoms had indicated the elevation of lithium level or the deterioration of renal function in the 2 weeks before the initiation of levofloxacin. It is therefore unlikely that an increase in the levels of lithium and creatinine occurred on or near the day when levofloxacin was initiated. Delirium has been reported with quinolones (unrelated to the use of lithium).<sup>6</sup> However, when our patient had been treated with chlorpromazine monotherapy, 200 mg/day, for 2 weeks to subside his first severe manic symptoms, he received levofloxacin, 300 mg/day, for bronchitis for 3 days in June 1993 without developing a delirious state. There-

fore, disturbed consciousness in this case does not seem to be attributable to delirium associated with levofloxacin.

Considering that administration of levofloxacin alone<sup>7</sup> or maintenance lithium therapy in itself<sup>8</sup> has rarely been associated with renal impairment, synergistic interaction between these 2 drugs might cause acute renal failure in this lithium-maintained patient, increasing serum lithium concentration. On the other hand, while there have been 2 case reports of tetracycline-associated lithium toxicity, a study in 14 volunteers actually found a slight but significant decline in serum lithium level associated with tetracycline use.<sup>8</sup> Thus, the potential for the interaction between levofloxacin and lithium warrants further study. We hope that this case will alert clinicians to the possibility of severe lithium toxicity after prescribing levofloxacin to patients receiving long-term lithium therapy.

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Hitoshi Takahashi, M.D.  
Hisashi Higuchi, M.D.  
Tetsuo Shimizu, M.D.

Akita University School of Medicine  
Akita-City, Japan

#### Colon Perforation and Peritonitis Associated With Clozapine

**Sir:** The antipsychotic clozapine can cause many adverse effects, most notably agranulocytosis and seizures. In addition to such effects on the hematopoietic system and the central nervous system, clozapine can seriously affect the gastrointestinal system: deaths from bowel obstruction,<sup>1</sup> severe fecal impaction,<sup>2</sup> and necrotizing colitis<sup>3</sup> have been reported. To increase awareness of clozapine's potent effects on the gut, we describe a case of a perforated colon and peritonitis associated with clozapine. Our patient survived, albeit with a markedly reduced quality of life.

**Case report.** Mr. A, a 49-year-old man with schizophrenia of the paranoid subtype and a history of long-standing constipation, presented to an emergency department with acute onset of severe abdominal pain. Mr. A's only medications on arrival were clozapine, 200 mg p.o. b.i.d., and a small nightly dose of lorazepam. Clozapine had been started 6 weeks prior to presentation during a psychiatric hospitalization. Mr. A had never received clozapine before, and his chronic problems with constipation had clearly become worse over the course of the 6 weeks on clozapine treatment. Despite repeated complaints

about worsening constipation by Mr. A and his family, no countermeasures were taken. In the emergency department, sepsis and a perforated bowel with massive fecal peritonitis were diagnosed, requiring emergency hemicolectomy and colostomy. Unfortunately, he sustained a massive right-sided cerebrovascular accident perioperatively, resulting in dense hemiplegia. When evaluated several months after the bowel perforation, Mr. A was psychiatrically stable; he showed only mild social uneasiness and nondisturbing faint auditory hallucinations on risperidone, 3 mg p.o. q.h.s., which he had been switched to after his emergency surgery.

Although constipation, nausea, and vomiting are recognized side effects of clozapine,<sup>4</sup> they are often considered more a nuisance than a potentially life-threatening problem. This contrasts with the experience of Hayes and Gibler,<sup>1</sup> who reported a patient death from bowel obstruction with aspiration of vomitus. They introduced a careful monitoring system after detecting a 60% prevalence of constipation with clozapine use in their state hospital population and developed a treatment protocol as well as a slow titration schedule.

What can we do to prevent fecal impaction and peritonitis in patients who receive clozapine? Diet modification and regular exercise should be encouraged to prevent constipation, although implementation of these recommendations is often a daunting task. It is important to have a low threshold for further investigation of potentially serious medical conditions in patients with chronic mental illnesses. These patients are often less able to describe their symptoms clearly, and frequently describe a variety of symptoms to relate their distress. Sometimes they are simply not believed because they are "psychiatric patients" and by extension considered "poor historians." Further complicating matters, some patients with schizophrenia seem to have an increased pain threshold. Fishbain<sup>5</sup> describes a psychotic patient who appeared well with no pain complaints but who died in septic shock from peritonitis secondary to a perforated ulcer. The physician caring for a patient on clozapine treatment must be ever vigilant for the potentially life-threatening sequelae of constipation.

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**Oliver Freudenreich, M.D.**  
**Donald C. Goff, M.D.**  
 Massachusetts General Hospital  
 Boston, Massachusetts

#### Treatment of Koro With Citalopram

**Sir:** We report a case of koro in a non-Asian patient that was treated with the selective serotonin reuptake inhibitor (SSRI) citalopram. Although reports of koro treatment with clomipramine exist,<sup>1</sup> this is, to our knowledge, the first report of koro treated with an SSRI.

**Case report.** Mr. A, a 56-year-old, single white man, sought treatment with the firm belief that his penis was shrinking and entering the abdomen, arousing great anxiety. This belief led him to pull his penis with the objective of avoiding retraction. These were his only complaints, and the application of the Structured Clinical Interview for DSM-III-R excluded other psychiatric diagnoses, such as schizophrenia, affective disorders, panic disorder, or obsessive-compulsive disorder, even subclinical. He had no organic disease or any other symptoms of body dysmorphic disorder (BDD). Mr. A had a broken heart and was concerned about his sexual functioning just before the symptoms of koro appeared. He reported a previous episode with the same complaints when he was 19 years of age, after feeling anal pruritus when riding a horse. On that occasion, his symptoms disappeared when he pulled his penis. In the present episode, he was treated with amisulpride, 50 mg/day, which was discontinued owing to akathisia and lack of response. After that, he started treatment with citalopram, 10 mg/day, and showed remission of symptoms after 1 month. He received no other treatment. No symptoms were observed during his 2-year treatment with this medication. Citalopram was subsequently discontinued, and Mr. A is still without symptoms.

Formerly considered a syndrome linked to the Chinese culture, koro can be characterized by a fear that the penis will shrink or retract, which is often accompanied by a belief that this will lead to death, intense panic with physical signs of anxiety, and use of mechanical means to prevent penile retraction. The description of cases in non-Asians reinforced the general point of view that koro is culture related although not bound to only one culture. Outside of southeast Asia, koro is often incomplete and does not usually include the use of mechanical means to prevent genital retraction.<sup>2</sup> The present case, the first reported in a South American man, manifests all symptoms, including the utilization of mechanisms to prevent retraction, such as hanging his penis through the pocket while in social occasions, e.g., church. The DSM-IV considers that koro can be related to BDD,<sup>3</sup> which overlaps with and can be double coded in DSM-IV with delusional disorder, somatic type.<sup>4</sup> The treatment of BDD with serotonin reuptake inhibitors has been empirically demonstrated.<sup>5</sup> Successful treatment of koro with citalopram is consistent with this diagnostic possibility, although this effect may have been a placebo response, since the patient had a previous episode of koro that remitted spontaneously.

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**Jaime E. C. Hallak, M.D.**  
**José A. S. Crippa, M.D.**  
**Antonio Waldo Zuardi, M.D., Ph.D.**  
 Hospital das Clínicas, Ribeirão Preto  
 São Paulo, Brazil