

## Letters to the Editor

### Special Thanks

As an addendum to our list of 1999 reviewers,<sup>1</sup> I extend special gratitude to the following reviewers whose service rendered on our behalf last year will bear fruit in our *Journal* this year. The commitment and expertise of these devoted individuals are the foundations upon which our scholarly and scientific excellence rests.

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### REFERENCE

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—A.J.G.

We report 3 cases in which patients developed schizophrenia and Gilbert's syndrome and discuss clinical aspects of Gilbert's syndrome in schizophrenic patients and the relationship between hyperbilirubinemia and schizophrenia.

**Case 1.** Mr. A, a 26-year-old single man, was diagnosed with schizophrenia at age 23 and admitted to the Shimane Medical University Hospital (Izumo, Japan). At that time, mild hyperbilirubinemia (total bilirubin level = 2.8 mg/dL, direct bilirubin level = 0.3 mg/dL), predominantly unconjugated, was first diagnosed on a routine laboratory test at admission and led us to suspect Gilbert's syndrome. After admission, Mr. A's psychiatric symptoms were well controlled by neuroleptic treatment. Laboratory tests of blood bilirubin levels showed an improvement 2 weeks after admission (total bilirubin level = 0.5 mg/dL, direct bilirubin level = 0.2 mg/dL). At the age of 26, coincident with discontinuation of antipsychotic medication, Mr. A experienced exacerbation of the psychotic condition and recurrent hyperbilirubinemia (total bilirubin level = 3.4 mg/dL, direct bilirubin level = 0.4 mg/dL) with a diagnosis of Gilbert's syndrome. He was readmitted to the Shimane Medical University Hospital in a severely psychotic state. Mr. A's psychotic condition has improved during the past 6 months with the administration of neuroleptics. Laboratory tests of blood bilirubin levels also showed improvement (total bilirubin level = 0.5 mg/dL, direct bilirubin level = 0.2 mg/dL). Mr. A experienced no relapse of psychotic condition with concomitant re-increase of unconjugated bilirubin levels.

**Case 2.** Mr. B, a 33-year-old single man, was diagnosed with schizophrenia at age 25, at which time treatment with neuroleptics was started. Coincident with the onset of psychosis, hyperbilirubinemia (total bilirubin level = 2.3 mg/dL, direct bilirubin level = 0.3 mg/dL), predominantly unconjugated, was first diagnosed on a routine laboratory test and led us to suspect Gilbert's syndrome. At the age of 30 years, Mr. B experienced exacerbation of the psychotic condition. He was admitted to the Shimane Medical University Hospital. Findings from laboratory examinations of serum and urine were normal, except the abnormal bilirubin level (total bilirubin level = 2.8 mg/dL, direct bilirubin level = 0.4 mg/dL). Mr. B's psychotic condition improved for 2 months with the administration of neuroleptics. This psychopathologic change was accompanied by a clear improvement of hyperbilirubinemia (total bilirubin level = 0.6 mg/dL, direct bilirubin level = 0.2 mg/dL). Mr. B experienced no relapse of psychotic condition with concomitant re-increase of unconjugated bilirubin levels.

**Case 3.** Mr. C, a 23-year-old single man, began to hear a voice commenting on his behavior and telling him to kill himself when he was 21 years old. He exhibited psychomotor excitement and delusions of persecution. Mr. C was admitted to the Shimane Medical University Hospital. He was diagnosed with schizophrenia, at which time treatment with neuroleptics was started. Coincident with the onset of psychosis, hyperbilirubinemia (total bilirubin level = 3.0 mg/dL, direct bilirubin level = 0.4 mg/dL), predominantly unconjugated, was first diagnosed on a routine laboratory test and led us to suspect Gilbert's syndrome. Mr. C's psychotic condition improved for 5

### Schizophrenia-Associated Idiopathic Unconjugated Hyperbilirubinemia (Gilbert's Syndrome): 3 Case Reports

**Sir:** Idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome) is a relatively common congenital hyperbilirubinemia occurring in 3% to 7% of the population.<sup>1-3</sup> Recently, it was reported that schizophrenic patients showed a significantly higher frequency of hyperbilirubinemia relative to patients with other psychiatric disorders and the general healthy population.<sup>4</sup> However, there has been only one previous case report of Gilbert's syndrome occurring in a schizophrenic patient.<sup>5</sup>

months with the administration of neuroleptics. This psychopathologic change was accompanied by a clear improvement of hyperbilirubinemia (total bilirubin level = 0.6 mg/dL, direct bilirubin level = 0.2 mg/dL). Mr. C experienced no relapse of psychotic condition with concomitant re-increase of unconjugated bilirubin levels.

All 3 patients presented above were diagnosed as having schizophrenia (DSM-IV) by the Structured Clinical Interview for DSM-IV<sup>6</sup> and showed mild chronic or recurrent unconjugated hyperbilirubinemia with otherwise normal liver function test results. In the absence of structural liver disease or hemolysis, the occurrence of unconjugated hyperbilirubinemia with normal conjugated bilirubin concentration is a symptom of Gilbert's syndrome.<sup>7</sup>

It is, of course, unlikely that the simultaneous occurrence of the exacerbation of hyperbilirubinemia with the emergence of schizophrenia in the 3 cases presented here was more than mere coincidence. However, some evidence suggests that the co-occurrence might not be coincidental. First, the exacerbation and remission of the hyperbilirubinemia closely correlated with the psychosis. When all 3 patients stopped taking their medications, their hyperbilirubinemia, as well as the symptoms of psychosis, returned. Second, it has been reported that schizophrenic patients showed a significantly higher incidence of hyperbilirubinemia than patients with other psychiatric disorders.<sup>4</sup> We also observed that patients with schizophrenia frequently presented with an increased plasma bilirubin concentration when admitted to the hospital (unpublished data, 1999). We think that this phenomenon was possibly not followed up because only a slight increase in plasma bilirubin levels—which, in the present cases, had decreased in most instances to a normal range at reevaluation—is observed in most schizophrenic patients with hyperbilirubinemia.

It has not been clarified to date whether stress and fasting can provoke hyperbilirubinemia in persons who have no genetic disposition for Gilbert's syndrome. This leads to the question of whether a genetic disposition for Gilbert's syndrome or, especially, the risk of a deficiency in glucuronyl transferase activity may be elevated in schizophrenic patients. On the other hand, hemolysis can cause an increase in plasma bilirubin levels. Some schizophrenic patients are known to show altered red blood cell membranes,<sup>8</sup> which, in turn, might elevate plasma bilirubin concentration. Treatment with neuroleptics seems to normalize the phospholipid alterations of the red cell membrane in schizophrenic patients.<sup>9</sup> In addition, estrogen provides protection against hyperbilirubinemia, especially Gilbert's syndrome,<sup>10,11</sup> influences dopamine metabolism,<sup>12</sup> and is thought to play a protective role in the onset of schizophrenia.<sup>12,13</sup>

Certainly, further studies are necessary to elucidate the possible association between Gilbert's syndrome and schizophrenia.

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#### Effectiveness of Risperidone in Simple Schizophrenia: A Single Case Report

**Sir:** Risperidone has been reported to be effective in ameliorating the negative symptoms of schizophrenia.<sup>1</sup> However, there have been no reports describing the treatment of simple schizophrenia with risperidone. The concept of simple schizophrenia has been considered controversial, and research criteria for simple deteriorative disorder (simple schizophrenia) are included in Appendix B of DSM-IV.<sup>2</sup> Criteria Sets and Axes Provided for Further Study.<sup>3</sup>

I report a case of simple schizophrenia that met DSM-IV research criteria for simple deteriorative disorder. The patient significantly improved following the administration of risperidone in an open clinical trial.

**Case report.** Mr. A, a 15-year-old boy, was admitted to our hospital with disheveled, long hair and offensive-smelling clothes. Case history revealed that in his childhood, he was cheerful, associated with his friends and family, and appeared to be an ordinary child. Mr. A did not experience any significant problems with his school studies and related well with his friends in elementary school. However, at the age of 12 years, he gradually became more unsociable with his friends and family and displayed an increased truancy rate. Mr. A showed a gradual loss of interest in previous activities; for example, he showed no emotion when viewing a television program that had previously made him laugh. In addition, 2 years prior to his admission, he isolated himself in his room, which was unkempt, and spent his time aimlessly and unproductively. His personal hygiene habits deteriorated as evidenced by his refusal to bathe or change his clothes. Mr. A appeared to be unaware of his strange and erratic

behavior; indeed, whenever his family confronted him about his behavior, he responded angrily and attributed all of his problems to his family.

Upon Mr. A's admission to our hospital, the attending psychiatrist recognized poverty of speech and avolition, although Mr. A had been speaking and laughing to himself 1 year prior to admission. The detailed questioning of his family, however, did not show clear evidence of his hallucinations and delusions. Mr. A had no history of substance abuse or family history of mental illness. The preliminary diagnosis, simple deteriorative disorder (DSM-IV), was given based on his clinical symptoms and the course. Mr. A was started on risperidone, 2 mg/day, on the day of admission, and this dosage was increased to 3 mg/day the following week. He did not report any significant side effects and began to show clinical improvement. He voluntarily took a bath during the second week of treatment, and he accepted his admission to the hospital despite his initial resistance to this action. Mr. A became more expressive during the third week, and his anger against his family gradually abated. This abatement was typified by his saying, "I don't know why, but I don't get angry with my father these days." Furthermore, he gradually began to socialize with people, and his avolition and poverty of speech showed marked improvement.

Mr. A was discharged after a 3-month hospitalization, and his family said, "He has returned to his former self: he cleans his room, takes a bath, talks to us, displays a cheerful disposition, and socializes with his friends." His total Negative Syndrome Scale<sup>3</sup> score was 27 when he was admitted, and on discharge it was 13, a clinically significant reduction. During hospitalization, neurologic examination and laboratory tests ruled out the presence of organic syndromes. Six months after Mr. A's discharge, his condition has remained stable with the medication unchanged.

Schizoid or schizotypal personality disorder should first be differentiated from simple schizophrenia because the disorders often have overlapping symptoms. This case, however, exhibited a marked decline in interpersonal, self-care, and school functioning over a period of more than 2 years. This decline is not indicative of personality disorders, which are represented by lifelong patterns without deterioration of functioning. Schizophrenia and other psychotic disorders were ruled out because of the absence of positive symptoms, such as psychosis and delusions. However, this diagnosis should be considered tentative, since information obtained about a patient from his or her family may not be accurate and can be biased. It may be possible that this patient had psychotic symptoms, but simply failed to disclose them to others. Thus, to strictly rule out personality disorders and schizophrenia, the patient must be followed longitudinally.

Depression was ruled out for our patient because he had no depressive symptoms during his course except for diminished interest and avolition. The most difficult problem in diagnosing simple schizophrenia may be differentiating an individual with the disorder from an individual without a mental disorder in that the negative symptoms of simple schizophrenia may be on a continuum with normality. In fact, it was difficult to distinguish the illness from the patient's lazy and sluggish life, although he met both DSM-IV criteria and Black and Boffeli's<sup>4</sup> proposed criteria for the clinical symptoms and the course of illness.

Although the confounding effect of hospitalization should not be ruled out, this case, in which the patient greatly improved following the administration of risperidone, potentially warrants the further study of the efficacy of risperidone in the treatment of simple schizophrenia. If risperidone proves to be effective for other cases of simple schizophrenia, clinicians might consider the use of risperidone for ambiguous cases that are difficult to

diagnose and in which patients are suspected of having simple schizophrenia.

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### Citalopram and Clozapine: Potential Drug Interaction

**Sir:** Clozapine, an atypical antipsychotic agent, appears to be metabolized, in part, by the cytochrome P450 (CYP) 1A2 and CYP3A3/4 enzymes. Clozapine's side effects include sedation, hypersalivation, constipation, seizures, weight-gain, and clozapine-induced agranulocytosis. Citalopram is a newly released selective serotonin reuptake inhibitor (SSRI) that is thought to have a favorable drug interaction profile secondary to weak or negligible inhibition of cytochrome P450 enzymes.<sup>1</sup> Other SSRIs have been reported to elevate serum clozapine levels by inhibiting CYP1A2 and CYP3A3/4 hepatic enzymes.<sup>2,3</sup> Reports in the literature suggest fluoxetine, sertraline, paroxetine, and fluvoxamine elevate serum clozapine levels to varying degrees.<sup>2-5</sup> We present a case of potential clozapine and citalopram drug-drug interaction.

**Case report.** Mr. A, a 39-year-old white man with a 20-year history of DSM-IV schizoaffective disorder, depressive type, was referred for a trial of clozapine after failing numerous trials of antipsychotic and antidepressant medications. He was switched from his regimen of lithium, 900 mg/day; risperidone, 3 mg/day; and bupropion, 300 mg/day to clozapine, 400 mg/day. He experienced a significant improvement in both positive and negative symptoms with clozapine, 400 mg/day. Mr. A experienced mild sedation and an increase in sleep secondary to clozapine over a 12-month period. Subsequently, he complained of feeling more depressed and citalopram, 20 mg/day, was initiated and increased to 40 mg/day after 2 weeks. One week after treatment with 40 mg/day of citalopram, Mr. A experienced worsening sedation, new-onset fatigue, enuresis, hypersalivation, and mild confusion. Serum clozapine levels were drawn and yielded the following results: clozapine, 360 ng/mL; norclozapine, 737 ng/mL; and a total serum clozapine level of 1097 ng/mL. The serum was analyzed according to high-performance liquid chromatography and gas chromatography methods.<sup>6</sup> The citalopram dose was reduced to 20 mg/day, which resulted in a complete resolution of the fatigue, enuresis, hypersalivation, and confusion within 2 weeks. The repeat serum clozapine levels 2 weeks after the reduction of citalopram were clozapine, 290 ng/mL; norclozapine, 502 ng/mL; and a total serum clozapine level of 792 ng/mL, representing a reduction of 19.44%, 31.88%, and 27.80%, respectively. Mr. A has remained on treatment with a combination of clozapine, 400 mg/day, and citalopram, 20 mg/day, with good results.



This case report suggests that citalopram at 40 mg/day may inhibit the metabolism of clozapine, resulting in higher serum concentrations compared with citalopram, 20 mg/day. The inhibition of CYP1A2 or CYP3A3/4 enzymes with citalopram may be dose related. Although serum clozapine levels without citalopram were not measured, the most compelling information is that the patient did not experience the above side effects while taking clozapine alone for 7 months or with 20 mg/day of citalopram. The results are comparable to the findings of Centorrino et al.<sup>5</sup> that showed moderate doses of fluoxetine, paroxetine, and sertraline resulted in a 43% increase in total serum clozapine concentration and a 10-fold greater risk of a total clozapine and norclozapine level higher than 1000 ng/mL. It is possible that the difference in serum clozapine level represents a random fluctuation of clozapine level, a pharmacodynamic interaction, or a compliance issue. Mr. A lives with his family, who closely monitor his medication compliance and report that he never misses a dose of any medication. Finally, this case report suggests that the combination of citalopram and clozapine should be closely monitored. Citalopram may increase serum clozapine levels, in some cases to potentially toxic levels.

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#### Gastrointestinal Adverse Effects With Divalproex Sodium and Valproic Acid

**Sir:** The retrospective analysis by Zarate et al.<sup>1</sup> comparing tolerability and efficacy of valproic acid and divalproex sodium in an inpatient psychiatric setting found a statistically significant difference in the incidence of gastrointestinal adverse effects. The authors also noted that the dosing frequency was significantly higher with valproic acid. It is important to note that the patients in both groups were naive to treatment with valproic acid and that the duration of data collection was less than 5 weeks.

Two previously published reports that were not reviewed by Zarate et al. compared efficacy and tolerability in patients stabilized on treatment with divalproex who were subsequently switched to valproic acid. In the first,<sup>2</sup> the impact of replacing divalproex sodium with valproic acid was evaluated retrospectively in 46 patients at a state facility for mentally retarded adults. Almost twice as many patients had gastrointestinal disorders during divalproex treatment (20%) as during valproic

acid therapy (11%). In the other study,<sup>3</sup> the impact of substitution of generic valproic acid for divalproex was evaluated in 47 adult psychiatric inpatients who had been stabilized on divalproex treatment at least 1 month prior. Dosing intervals remained unaltered for all but 2 patients, whose single doses of divalproex greater than 2 g were divided into twice-daily doses. Fourteen patients had gastrointestinal complaints during the month before the switch compared with 5 patients during the study period.

Experience within several facilities in Ohio has been consistent with these published reports. Divalproex was replaced by valproic acid on a milligram-per-milligram basis in 46 patients at Warrensville Developmental Center. The nursing staff was instructed to observe and report any untoward effects, and blood drug levels were obtained at 2 and 4 weeks after the replacement was ordered. The valproate levels of the clients remained consistent with their past levels. One client was switched back to divalproex because he refused to take the syrup and his previous dosage of divalproex (875 mg daily) could not be attained with 250-mg capsules of valproic acid. The estimated yearly savings to this facility was \$52,490.00.

At the Southern Ohio Correctional Facility, 52 patients were switched from divalproex to valproic acid over a period of 4 months. Adverse effects were monitored over the course of the interchange period. Four patients reported gastrointestinal upset secondary to valproic acid capsules; 3 of these patients were treated with antacid. Only 1 patient was switched back to divalproex. The projected savings to the institution was \$43,071.96 per annum.

Although the general practice might be to dose valproic acid more frequently than divalproex, increasing the dose frequency was not required when patients were switched from divalproex to valproic acid. The half-life of valproate is identical whether it is given as the prompt valproic acid or enteric-coated tablets.

We propose that a reasonable conclusion encompassing all of these observations might be that both divalproex and valproic acid cause a high incidence of gastrointestinal adverse effects. The incidence of adverse effects is higher when therapy is initiated with valproic acid; however, tolerance to these effects occurs with continued use of either agent. The higher incidence of adverse effects with valproic acid on initiation of treatment does not appear to preclude the use of this product for maintenance in most patients.

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#### Dr. Zarate Replies

**Sir:** In their letter, Wagner and colleagues report that, in contrast to our article,<sup>1</sup> they were able in an open-label fashion to successfully switch 98 inpatients from divalproex sodium to

valproic acid without an increased incidence in gastrointestinal side effects. On the basis of their observations and those of 2 other studies,<sup>2,3</sup> they conclude that these preparations are interchangeable and that switching from divalproex to the less costly form of the drug, immediate-release valproic acid, should be considered.

There are now an increasing number of reports on the replacement of divalproex sodium with valproic acid. Some reports suggest that the switch can be done successfully<sup>2,3</sup> and that substantial cost savings may be achieved.<sup>3,4</sup> Our study<sup>1</sup> and those of others<sup>5,6</sup> do not support that the conversion is well tolerated.

Wagner and colleagues discuss 2 main points: (1) that conversion can be done safely in a majority of cases and (2) that, as a result of successful conversion, substantial cost savings will be achieved. They report that they were able to successfully switch 98 inpatients at 2 large state institutions in Ohio from divalproex to valproic acid on a milligram-per-milligram basis. For site 1, (Warrensville Developmental Center), there is no mention of the rate of gastrointestinal side effects; there is only mention that 1 client was switched back to divalproex because of refusal to take the syrup form of the drug. At site 2 (the Southern Ohio Correctional Facility), only 7.7% of patients reported gastrointestinal side effects, of whom 3 were treated with antacids. Both sites 1 and 2 estimate substantial yearly cost savings with the conversion. There is no mention of whether the patients had any side effects, especially gastrointestinal side effects (site 1); what concomitant medications were received (sites 1 and 2); whether the patients were taking antacids (site 1); and the efficacy of valproic acid after the switch (sites 1 and 2).

The authors go on to estimate that the yearly savings at these 2 institutions would be \$95,561.96. However, the longest period of treatment with valproic acid at either institution was 4 months. No data are presented to support their conclusion of cost savings. Other factors that should be taken into account to estimate costs associated with a treatment include concomitant medications (especially histamine-2 antagonists or other drugs that may cause gastrointestinal side effects), relapse rates, length of stay, consultations, and efficacy increases.<sup>7</sup>

I disagree with the authors' conclusion that both divalproex and valproic acid have a "high" incidence of gastrointestinal side effects, that they are interchangeable, and that there are greater costs with the use of divalproex sodium over the long term. None of the above studies supports that significant cost savings are achieved with the conversion of divalproex therapy to treatment with valproic acid. In our study,<sup>1</sup> we compared the information obtained from the medical records of 150 inpatients treated with divalproex sodium with that of 150 inpatients treated with valproic acid. Information concerning which drug they were taking (divalproex sodium or valproic acid) was concealed. We found that patients treated with divalproex sodium were less likely to experience gastrointestinal side effects and to have discontinued their medication because of an adverse event than were patients treated with valproic acid.

Possible explanations for these discrepancies include nonsystematic sampling, different diagnostic groups studied, acuity of the diagnosis, how information on the presence or absence of side effects was collected, the concomitant medications used, the lack of a control group, and the lack of sufficient follow-up.

Clearly, further studies are needed to ascertain the rate of gastrointestinal side effects for these 2 preparations, how interchangeable they are, and in what circumstances they are interchangeable. In addition, it remains to be determined whether cost savings are truly associated with one drug over the other. Although there may be a subgroup of patients who tolerate the switch well, until safety and efficacy data become available, I

believe that a switch should not be routinely ordered. Instead, I recommend that treatment be individualized and that the final decision be left not to administrators but instead to the patient and the treating clinician.

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#### Misuse of the Term *Phenomenology*

**Sir:** The recent supplement<sup>1</sup> to the *Journal*, "Phenomenology and Treatment of Aggression Across Psychiatric Illnesses," is marred by a misuse of the term *phenomenology*. This problem is common in your journal, and I am writing to bring it to your attention.

*Phenomenology* is a very broad term that refers to all experience, normal and abnormal. In contrast, the term that should be used to refer to pathologic experience alone, as is obviously the intention in this supplement, is *psychopathology*.

For example, in the "Introduction," the editors plainly begin, "Aggression is a dimensional symptom . . ." Already, on line 1, from a phenomenologic vantage, there are 2 major problems with this supplement: (1) the claim that aggression is a dimension and (2) the claim that aggression is a symptom.

The claim that aggression is a dimension is not descriptive (phenomenological), but is rather a theory about aggression. For example, "the increased activity and agitation" (editors' terms) that we see in the aggression of a cat in a cat fight is qualitatively different from the calm, deliberate, and quiet aggression of a cat stalking its prey. Indeed, a single "dimension" of aggression cannot encompass these 2 very different forms of aggressive behavior. (I could go on—there are more than 2 qualitatively different forms of aggression—but I will not; then I would be performing a phenomenology of aggression, rather beyond the scope of this letter.) Theories ignore features of phenomena in order to focus on other aspects of the same phenomena. My point is that the editors have clearly chosen a theoretical path in this supplement and not a phenomenological one.

The claim that aggression is a symptom is also a theory and a very bad one at that. Aggression is much more than a symptom. Obviously, soldiers should be aggressive and so should trial lawyers, venture capitalists, and academic psychiatrists who are trying to get grants and publish. When we begin with the idea

that aggression is a symptom, we are guilty of pathologizing the normal, something we psychiatrists should vigorously avoid doing.

Another problem follows from the above two. The supplement editors claim to cover the spectrum of aggression from one end, "activity and agitation," to the other, "violent criminal behavior." However, concerning aggression, this is not "one end to the other," no matter how we construe it. For example, one end of a spectrum of aggression could begin with diminished aggression, "the meek and the mild"; on the other end, we would go on to "the violent," etc. Or one end could begin with healthy aggression, perhaps with concepts such as assertiveness, and the other would go on to unhealthy forms of aggression, such as violent, rageful murder.

The editors chose to avoid all of these problems with their reductionistic approach. Fine. Just don't call it phenomenology. It is not.

Finally, in fact this is the *Journal's* problem and not that of the editors of this particular supplement. Again and again, the editors of the *Journal* seem to prefer the term *phenomenology* when *psychopathology* is more appropriate. Editorial policy is wanting here and should be corrected. Yours is a wonderful journal, and you don't need to gussy up your papers with high-sounding language when more ordinary words will do (and even do a better job).

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**Low-Dose Lithium Augmentation of Divalproex in Geriatric Mania**

**Sir:** It is widely believed that antimanic efficacy with lithium requires doses at a level sufficient to achieve blood levels > 0.7 mEq/L,<sup>1</sup> although few data exist about bipolar patients who may respond to doses producing lower serum levels. In addition, as anticonvulsant mood stabilizers enter wider use, little is known about whether some bipolar patients respond preferentially to lithium or to combinations of lithium and anticonvulsants. We report 2 cases of geriatric mania that occurred after lithium discontinuation due to neurotoxicity. Subsequent anticonvulsants and/or atypical neuroleptics had little efficacy, but the addition of low-dose lithium to divalproex sodium led to dramatic improvement in both cases.

**Case 1.** Ms. A, a 76-year-old single white woman with a 56-year history of bipolar disorder and 6 prior episodes, had been stably maintained for more than 10 years on lithium monotherapy (900 mg/day) with an average serum lithium concentration of 0.9 mEq/L. Lithium overdosage during a breakthrough non-psychotic mixed state produced a serum lithium concentration of 2.66 mEq/L, which was ameliorated with hydration and drug cessation, but led to cognitive impairment persisting for several months. Dysphoria, agitation, anxiety, racing thoughts, and hopelessness continued despite trials of divalproex (1250 mg/day for > 6 weeks; peak serum valproate concentration = 61.6 ng/mL), olanzapine (10 mg/day for > 6 weeks), risperidone (1 mg/day for 1 week), paroxetine (30 mg/day for 6 weeks), and venlafaxine

extended release (75 mg/day for 4 weeks), alone and in combination. Augmentation of divalproex with lithium, 600 mg/day (serum lithium concentration = 0.63 mEq/L, serum creatinine concentration = 0.9 mg/dL), as the sole adjunctive agent produced improvement in mania, depression, and anxiety after 3 weeks with uncompromised cognitive status.

**Case 2.** Ms. B, a 71-year-old widowed white woman with a 36-year history of bipolar disorder and 10 lifetime affective episodes, had been stably maintained for the previous 4 years on lithium, 1200 mg/day, and carbamazepine, 400 mg/day, with a steady-state serum lithium concentration ranging from 0.78 to 0.85 mEq/L and serum carbamazepine concentration of 7.4 to 8.4 ng/mL. When medical illness produced malnutrition and dehydration, the patient self-discontinued carbamazepine only, resulting in ataxia, disorientation, and tremor (serum lithium concentration = 1.69 mEq/L; serum carbamazepine concentration was undetectable). Dysphoric mania with paranoid delusions occurred after lithium discontinuation. Inpatient efforts to restabilize with carbamazepine, 400 mg/day for > 4 weeks; divalproex, 1250 mg/day for > 4 weeks (serum valproate concentration = 87.6 ng/mL); and/or risperidone, 1 mg/day for > 4 weeks, were partly effective. Subsequently, the combination of divalproex with lithium, 900 mg/day (serum lithium concentration = 0.43 mEq/L; serum creatinine concentration = 0.7 mg/dL), led to marked improvement in mania and depression after 3 weeks.

Both cases demonstrate responsivity to lithium when lithium is reintroduced at lower doses after its abrupt discontinuation due to toxicity. Current theories about lithium's possible mechanism of action suggest it may play a unique role in G protein-mediated signal transduction of second messenger systems implicated in bipolar disorder.<sup>2</sup> It is possible that a minimum tissue concentration of lithium may be necessary for these physiologic events to occur. Bipolar patients intolerant of high-dose lithium, especially geriatric patients for whom lower-dose psychotropic drugs may be necessary,<sup>3</sup> may benefit from a combination of lithium and anticonvulsant mood stabilizers. Synergistic effects could also arise by different mechanisms, since lithium and divalproex modulate common biochemical targets.<sup>2</sup> In light of recently observed better outcomes for elderly bipolar patients with serum lithium levels  $\geq$  0.8 mEq/L,<sup>4</sup> it would be useful to determine when lower doses may effectively augment other therapies or identify patients who may selectively respond to low-dose lithium treatment. The potential for lithium to confer a unique therapeutic advantage for certain bipolar patients, as well as its role in combination treatment for acute mania, warrants further study.

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