Adding Lithium or Anticonvulsants to Antipsychotics for the Treatment of Schizophrenia: Useful Strategy or Exercise in Futility?

Leslie Citrome, M.D., M.P.H.

Clinicians often go to heroic lengths to find effective treatment strategies for their patients suffering from treatment-resistant schizophrenia. These approaches include polypharmacy with other antipsychotics as well as adjunctive medication strategies with mood stabilizers such as lithium or anticonvulsants. The hope is for an enhancement of pharmacodynamic effects so that treatment response is perhaps quicker in onset, more robust, and enduring. At first glance, adding lithium or valproate appears reasonable. After all, the combination of antipsychotics with lithium or valproate has received FDA approval for the treatment of bipolar mania, supported by evidence that combination treatment increases the opportunity for both response and remission.[1] There is often hope that this treatment strategy would be useful in managing aggression, and this quite likely influences the prescription of adjunctive lithium or anticonvulsants for patients with schizophrenia.[2] High utilization rates have been observed among inpatients in intermediate and long-term care settings such as the facilities operated by the New York State Office of Mental Health, where the percentage of inpatients with schizophrenia receiving adjunctive lithium or anticonvulsants has remained at approximately 50% since 1999.[3] This does not include patients with schizoaffective disorder, in whom the use of adjunctive lithium or anticonvulsants in 1998 was substantially higher, at 74%,[4] and in whom the target symptoms may have been a disturbance in mood; further discussion of schizoaffective disorder and its management can be found elsewhere.[5]

Unfortunately, in contrast to bipolar mania, compelling evidence supporting the combination of antipsychotics with lithium or anticonvulsants does not exist for schizophrenia. Indeed, the recent literature is replete with descriptions of trials that have failed to show advantages for combining antipsychotics with anticonvulsants.[3] One example is the recently reported large trial[6] conducted by Abbott Laboratories, makers of an extended-release formulation of divalproex sodium, that tested the efficacy and safety of adding this agent to olanzapine or risperidone in patients with acute exacerbations of schizophrenia. This was a 12-week, randomized, double-blind, parallel-group, multi-center trial that enrolled 402 patients. It was designed to replicate the positive findings of an earlier and smaller 4-week trial[7] that used a delayed-release formulation of divalproex and that demonstrated an acceleration of antipsychotic response with the combination strategy. However, this time, no efficacy advantages for combination treatment were evidenced. Moreover, antipsychotic monotherapy was actually superior to adjunctive valproate on negative symptoms at most of the time points at which these symptoms were assessed. The overall lack of benefit of adjunctive divalproex in this study is consistent with the latest iteration of the Cochrane Library systematic review, published in 2008, which found little evidence to support the use of adjunctive valproate in the management of schizophrenia,[8] not to mention the potential for additional adverse events beyond that expected with the use of antipsychotics alone.

Additional disappointment emerged from a clinical research program conducted by another manufacturer, GlaxoSmithKline, makers of lamotrigine. On the basis of initial positive reports from small studies, 2 similarly designed, multicenter, randomized, double-blind, 12-week, parallel-group studies[9] (N = 209 and N = 210) of adjunctive lamotrigine were conducted in patients with schizophrenia who had not responded adequately to second-generation antipsychotics alone. Overall, mean Positive and Negative Syndrome Scale total scores improved in both studies and did not differ between treatment groups. Secondary objectives that evaluated additional measures of global response, negative symptoms, depressive symptoms, and quality of life also failed to support a claim for greater clinical effectiveness with adjunctive lamotrigine. However, there may be a role for adjunctive lamotrigine specifically in patients with treatment-refractory schizophrenia who are also receiving clozapine, as demonstrated by a meta-analysis[10] in which, among a total of 161 randomized patients across 5 trials, lamotrigine was superior to placebo augmentation.

The other relevant agents used adjunctively with antipsychotics and for which controlled studies exist are carbamazepine, topiramate, and lithium.[3] Regrettably, these trials are small and their results conflicting, and, with few exceptions, they do not offer much guidance. Many of the published studies suffer from a variety of methodological flaws such as lack of control for confounds (for example, affective symptomatology, as seen when studies include patients with schizoaffective disorder), inadequate duration (usually too short), or inappropriate target populations such as patients with acute exacerbations of schizophrenia rather than treatment-refractory schizophrenia with persistent residual symptoms.

There are signals that carbamazepine may be useful in suspiciousness, uncooperativeness, and excitement,[11] but confirmatory data are lacking,[12] and the Cochrane group concluded that "adjunctive carbamazepine cannot be recommended for routine clinical use for the treatment of schizophrenia."[12] Topiramate is intriguing because of its association with weight loss,[13] and small, controlled studies for its adjunctive use in managing the symptoms of schizophrenia are promising,[14,15] but cognitive dulling may be of significant clinical importance in a patient who may already be cognitively impaired.[16]

Lithium is perhaps the best-known mood stabilizer, as it has been a foundational treatment for bipolar disorder for decades. Although early studies showed adjunctive lithium to be somewhat useful in treating schizophrenia, later and better-designed trials did not.[3] A comprehensive Cochrane review of randomized clinical trials concluded that, despite some evidence supporting the efficacy of lithium augmentation among 11 studies testing this, overall results were inconclusive.[17] A niche use for lithium can be as an adjunct to clozapine to prevent neutropenia, as demonstrated in case reports and in a retrospective case series.[18] However, there are no published reports of prospective controlled studies examining this use.

Adverse effects associated with valproate include sedation, gastrointestinal complaints, increased weight, menstrual disturbances, tremor, alopecia, thrombocytopenia, hyperammonemia, and elevation of hepatic transaminase and serum amylase.[19] Adverse effects associated with carbamazepine include leukopenia, diplopia, uncoordination, sedation, weight gain, and benign rash.[20] Lamotrigine can be associated with skin rash, dizziness, headache, diplopia, ataxia, nausea/vomiting, blurred vision, somnolence, and rhinitis.[21] Topiramate can be associated

with paresthesias/numbness, nausea and vomiting, cognitive impairment, headache, dizziness, and sedation/drowsiness/fatigue/somnolence.[16] Lithium's acute toxic effects include nausea, diarrhea, blurred vision, polyuria, dizziness, a fine resting tremor, muscle weakness, and drowsiness.[22] Thus, combining any of these agents with antipsychotics provides many opportunities for therapeutic misadventures.

While this review indicates little evidence for the effectiveness of adjunctive mood stabilizers in most patients with schizophrenia, there may be individual patients who benefit from anticonvulsants or lithium. These are patients who appear to benefit when these agents are added, deteriorate when they are withdrawn, and improve again when they are reinstated, thus making the case for an "N of 1" efficacy trial.[23] Before adjunctive agents are contemplated, the clinician should consider other possibilities such as the use of clozapine, a proven medication for treatment-resistant schizophrenia[24] as well as for schizophrenia associated with aggression.[25] Diagnostic confounds that might contribute to treatment resistance, such as comorbid psychiatric or somatic disorders, or substance or alcohol use, should be accounted for as well. Lack of treatment response to an antipsychotic may also be due to inadequate dose or duration of treatment, as well as inadequate adherence; in these circumstances, adding another medication is unlikely to be useful and needlessly complicates management.

If adjunctive mood stabilizers are considered, the clinician should outline a solid rationale for combination therapy when presenting this option to the patient and documenting this plan in the medical record. In addition, if a mood stabilizer is tried empirically and is not effective, it should be expeditiously discontinued. Given the lack of evidence for adjunctive mood stabilizers in schizophrenia, the clinician will shoulder the burden of demonstrating the need for this treatment and its effectiveness.

From the New York University School of Medicine, Department of Psychiatry, and the Nathan S. Kline Institute for Psychiatric Research, Orangeburg, N.Y.

Dr. Citrome is a consultant for, has received honoraria from, or has conducted clinical research supported by Abbott, AstraZeneca, Avanir, Azur, Barr, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Jazz, Pfizer, and Vanda.

Corresponding author and reprints: Leslie Citrome, M.D., M.P.H., Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Rd., Orangeburg, NY 10962 (e-mail: citrome@nki.rfmh.org).

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