Stabilizing glutamate transmission may benefit some patients with treatment-resistant schizophrenia

Current PSYCHIATRY

WHEN CLOZAPINE IS NOT ENOUGH

Augment with lamotrigine?

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Current antipsychotics are reasonably effective in treating positive symptoms, but they do less to improve the negative and cognitive symptoms[1] that contribute to patients' long-term poor functional capacity and quality of life.[2] So what do psychiatrists do in clinical practice to mitigate antipsychotics' limitations? We augment.

Schizophrenia patients routinely are treated with polypharmacy—often with antidepressants or anticonvulsants—in attempts to improve negative symptoms, aggression, and impulsivity.[3] Most adjuncts, however—including divalproex, antidepressants, and lithium—have shown very small, inconsistent, or no effects.[4,5] The only agent with a recent meta-analysis supporting its use as augmentation in treatment-resistant schizophrenia is lamotrigine,[6] an anticonvulsant approved for use in epilepsy.[7]

This article examines the evidence supporting off-label use of lamotrigine as an augmenting agent in schizophrenia and explains the rationale, based on lamotrigine's probable mechanism of action as a stabilizer of glutamate neurotransmission.

Is lamotrigine worth trying?

Some 20% of schizophrenia patients are considered treatment-resistant, with persistent positive symptoms despite having undergone ≥2 adequate antipsychotic trials.[8] Evidence suggests

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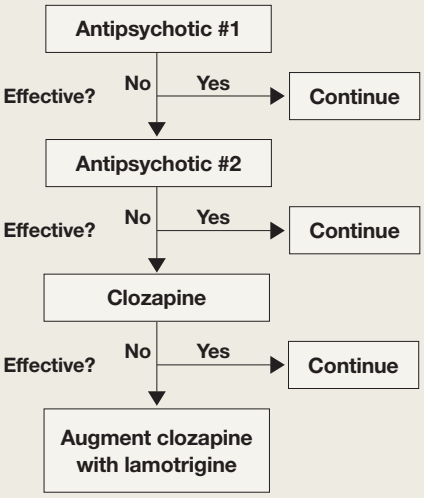
Adjunctive lamotrigine

Clinical Point

Evidence does not support routine use of lamotrigine in patients taking antipsychotics other than clozapine

Figure 1

An evidence-based approach to treatment-resistant schizophrenia



Treatment-resistant schizophrenia is defined as residual positive symptoms after ≥2 adequate antipsychotic trials. Evidence supports trying clozapine as the next step.[4] When patients show an inadequate response to clozapine, a meta-analysis of 5 controlled trials[6] indicates that lamotrigine may be a useful first-line adjunct.

clozapine then should be tried,[4] but approximately one-half of treatment-resistant patients do not respond to clozapine. Treatment guidelines are limited for these 10% of schizophrenia patients with an inadequate response to available therapies, including clozapine.[4]

In a meta-analysis of 5 controlled trials in patients with treatment-resistant schizophrenia, adjunctive lamotrigine was shown to significantly reduce Positive and Negative Syndrome Scale (PANSS) total scores, positive symptom subscores, and negative symptom subscores.[6] In these trials, lamotrigine was added to various antipsychotics, including clozapine. Based on the results—as outlined below—we suggest:

- In treatment-resistant patients with residual symptoms while taking clozapine, lamotrigine given in dosages ≥200 mg/d could be a first-line adjunct (***Figure 1***).
- Lamotrigine augmentation also might help patients whose positive symptoms are adequately controlled but who have persistent negative and/or cognitive symptoms.
- Evidence does not support routine use of lamotrigine in patients taking antipsychotics other than clozapine.

Managing side effects. Lamotrigine is generally well tolerated; in the meta-analysis, nausea was the only side effect more common with lamotrigine (9%) than with placebo (3.9%).[6] Close follow-up is required, however, as a few case reports have noted worsening positive symptoms when lamotrigine was added to antipsychotics.[9,10]

Lamotrigine produces a skin rash in approximately 10% of patients; the rash usually is benign but may be severe, including the potentially fatal Stevens-Johnson syndrome.[11] In the meta-analysis, rash was no more likely in patients receiving placebo (3%) than those receiving lamotrigine (2.2%), and no serious rashes were reported.[6] Even so, lamotrigine needs to be titrated upwards very slowly over weeks, and patients must be able to monitor for rash.

Why consider lamotrigine?

During clinical trials of lamotrigine for epilepsy, patients showed improved mood[12] as is seen with other anticonvulsants such as valproate and carbamazepine.[13] A series of randomized trials then demonstrated lamotrigine's effectiveness in treating patients with bipolar I disorder, especially during depressive episodes,[14,15] and the FDA approved lamotrigine for maintenance treatment of bipolar I disorder.[16] In those early studies, lamotrigine also improved bipolar patients' quality of life and cognitive function in addition to showing mood-stabilizing properties.[12]

The glutamate hypothesis. Lamotrigine is an inhibitor of voltage-gated sodium channels and has been shown to inhibit the excessive synaptic release of glutamate.[17] Glutamate is the primary excitatory neurotransmitter for at least 60% of neurons in the brain, including all cortical pyramidal neurons. A large body of evidence implicates dysfunctional glutamate signaling in the pathophysiology of schizophrenia.[18]

For example, phencyclidine (PCP) and ketamine—antagonists of one subtype of

glutamate receptor, the N-methyl-D-aspartate (NMDA) receptor—are well known to produce positive psychotic symptoms, negative symptoms, and cognitive dysfunction.[19] This led to a long-held hypothesis that schizophrenia is caused by too little glutamate. However, ketamine and PCP also increase the release of glutamate at synapses that then can act on glutamate receptors other than the NMDA receptor, which suggests that *too much* glutamate also may be involved in schizophrenia.

Too little or too much glutamate? These competing hypotheses could both be at least partially true, suggesting an "inverted-U" pattern of glutamate signaling (***Figure 2***). Because glutamate is involved in most cortical functions, too little glutamate can cause cognitive and processing deficits such as those seen in schizophrenia. On the other hand, too much glutamate can be toxic to neurons and may be a factor in neurodegeneration, such as in Alzheimer's disease.[20] Indeed, schizophrenia may be associated with gradual neurodegeneration.[21]

Glutamate stabilization?

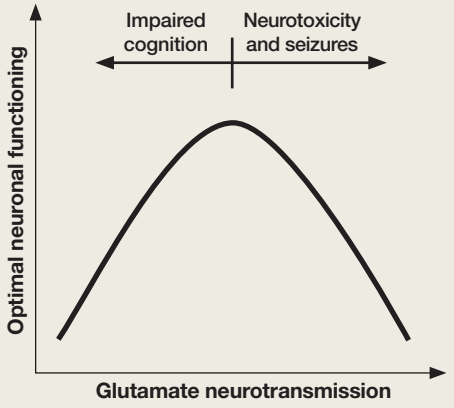
Because lamotrigine prevents excessive glutamate release at synapses, it stabilizes neuronal membranes by preventing toxicity from too much glutamate without interfering with glutamate's normal functions.[22] Thus, lamotrigine may have potential to maintain optimal glutamate signaling in patients with schizophrenia.

In 16 healthy volunteers, a 300-mg dose of lamotrigine was significantly more effective than placebo in reducing ketamine-induced positive symptoms, as assessed by the Brief Psychiatric Rating Scale positive symptoms subscale ($P < .001$). Lamotrigine pretreatment also reduced negative symptoms and improved learning and memory.[23]

More recently, lamotrigine pretreatment was shown to prevent many ketamine-induced changes on functional MRI.[24] Few antipsychotics have clinically significant effects on ketamine-induced symptoms—especially in a single dose—although repeated dosing with clozapine attenuates some ketamine-induced effects.[25]

Figure 2

Inverted U-curve may explain dysfunctional glutamate signaling in schizophrenia



Both too little or too much glutamate may play a role in schizophrenia's pathophysiology. Glutamate, the major excitatory neurotransmitter of the cerebral cortex, is involved in most cognitive functions. Too little (or glutamate inhibition) can impair cognition, whereas too much can lead to seizures, neurotoxicity, and cell death.

Given the limitations of available antipsychotics, adding a drug such as lamotrigine—which may modulate and stabilize the glutamate system—could be effective in treatment-resistant schizophrenia.

What is the evidence?

Case reports and open-label case series first showed that lamotrigine augmentation could be effective in treatment-resistant schizophrenia patients receiving clozapine.[26-28] One naturalistic case series also included patients receiving olanzapine or risperidone and suggested greater improvement with lamotrigine augmentation in patients on clozapine.[26]

Controlled trials. In a placebo-controlled trial, Tiihonen et al[29] reported significantly lower ratings of positive symptoms—but not negative symptoms—after 38 treatment-resistant schizophrenia patients on clozapine received adjunctive lamotrigine, 200 mg/d, for 14 weeks (***Table 1, page 44***).

A subsequent controlled trial in which Kremer et al[30] added lamotrigine, ≤400 mg/d, showed significant improvements in positive and negative symptoms among 31

Clinical Point

Lamotrigine has been shown to inhibit the excessive synaptic release of glutamate, which is involved in most cortical functions

Adjunctive lamotrigine

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Lamotrigine given at doses ≥200 mg/d appeared in controlled trials to be more efficacious than lower dosages

Table 1

Lamotrigine augmentation: 5 double-blind, placebo-controlled trials

Trial duration	Patient diagnosis (number)	Antipsychotic(s)	Lamotrigine (mg/d)	Results
14 weeks (Tiihonen et al, 2003[29])	Treatment-resistant schizophrenia (n=34)	Clozapine	200	Significantly reduced psychosis ratings, with no significant improvement in negative symptoms
10 weeks (Kremer et al, 2004[30])	Treatment-resistant schizophrenia (n=38)	Conventional and atypical, including clozapine	≤400	Significant improvements with all antipsychotics, especially clozapine, in positive and negative symptoms*
8 weeks (Akhondzadeh et al, 2005[31])	Schizophrenia (n=36)	Risperidone	150	Significant improvement in negative symptoms and cognition; less improvement in positive symptoms
12 weeks, multicenter (Goff et al, 2007[32])	Schizophrenia, schizoaffective patients with residual symptoms (n=217+212)	Conventional and atypical, including clozapine	100 to 400	No significant improvement in any symptom domain; improved negative symptoms only in study 1 and cognitive symptoms only in study 2
24 weeks (Zoccali et al, 2007[33])	Treatment-resistant schizophrenia (n=51)	Clozapine	≤200	Significant improvement in positive and negative symptoms as well as some cognitive symptoms

* Significance achieved only in study completers, not in the last-observation-carried-forward analysis

treatment-resistant schizophrenia patients who completed the 10-week study. Patients were taking conventional and atypical antipsychotics, including clozapine. All groups improved, but the study was not powered to detect differences among the groups.

A third trial by Akhondzadeh et al,[31] augmenting risperidone with lamotrigine, 150 mg/d, resulted in modest improvements in negative and cognitive symptoms and slight improvement in positive symptoms.

Multicenter trials. Preliminary trials led to 2 randomized, double-blind, multicenter studies. In a total of 429 schizophrenia outpatients with residual psychotic symptoms on atypical antipsychotics, lamotrigine, 100 to 400 mg/d, or placebo was added for 12 weeks.[32] The combined results failed to show significant improvement with adjunctive lamotrigine in any symptom domain compared with placebo. One study showed some improved negative symptoms, and the other showed improved cognitive symptoms.

Possible reasons for these negative results were unclear, although:

- a relatively large placebo response, compared with other studies, suggests a "failed" clinical trial
- the small number of patients receiving clozapine in this study suggests that they may have been less treatment-resistant than those enrolled in prior studies.

Meta-analysis. A meta-analysis of data from these 5 randomized, controlled trials found the "positive, negative, and general psychopathology subscale scores as measured with the PANSS … showed significant difference favoring adjuvant lamotrigine" (***Table 2***).[6] As for study limitations, the authors noted that effectiveness data could be usefully analyzed in <70 of the 537 patients from the controlled trials, and "the small mean decrease in scores may not be really clinically relevant."[6] Thus, they said, caution is warranted in translating these results to clinical practice.

One more trial. Since the meta-analysis, an additional placebo-controlled trial has been reported.[33] In this 24-week trial, lamotrigine

augmentation, ≤200 mg/d, was statistically more effective than placebo in reducing positive and negative symptoms in 51 stable treatment-resistant patients on clozapine. Cognitive function also improved.

Only treatment-resistant patients?

In controlled trials, lamotrigine augmentation has had the greatest effect on positive and negative symptoms in treatment-resistant schizophrenia patients, especially those on clozapine. Could lamotrigine augmentation be of benefit only in treatment-resistant schizophrenia?

Analysis of trial findings. As mentioned, outpatients who comprised the majority of subjects in the 2 large "negative" (or possibly failed) trials[32] might have been less treatment-resistant than subjects in the other trials. Lower mean lamotrigine dosages (205 mg/d and 241 mg/d) also were used in the 2 negative trials and in the trial by Akhondzadeh et al (150 mg/d)[31]—compared with up to 400 mg/d in the trial by Kremer et al.[30] This suggests that insufficient dosing might have caused the nonsignificant findings.

Given schizophrenia's heterogeneity, treatment-resistant patients may represent a subgroup that has greater glutamatergic dysfunction, whereas patients who respond more completely to antipsychotics may have greater dopaminergic dysfunction. Thus, lamotrigine augmentation might be more beneficial in the subset of treatment-resistant patients. Lamotrigine or other glutamate stabilizers have been proposed to act as neuroprotective agents, slowing functional decline in chronic schizophrenia[34] (although long-term studies needed to test this hypothesis are unlikely to occur because of cost and time constraints).

Another hypothetical, yet intriguing, explanation for the greater effects of lamotrigine augmentation in patients on clozapine is a pharmacodynamic interaction between these 2 drugs. Clozapine (and possibly olanzapine) have been shown to enhance cortical glutamatergic transmission.[25] We propose that clozapine-induced boosting of glutamate in concert with stabilization of the glutamate system by lamotrigine improves neuronal functioning. Clinical trial data regarding lamotrigine augmentation of antipsychotics other than clozapine are needed to determine if the relationship between clozapine and lamotrigine is unique.

Table 2

How symptom scores changed with add-on lamotrigine in the meta-analysis of controlled trials

PANSS subscales: Individual items scored 1 to 7, with 1 = absent and 7 = extreme	Change [95% CI]*
Positive symptom subscale (max 49) Delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness, hostility	**-5.10 [-8.86, -1.34]**
Negative symptom subscale (max 49) Blunted affect, emotional withdrawal, poor rapport, passive-apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking	**-5.25 [-7.07, -3.43]**
General psychopathology subscale (max 112) Somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, active social avoidance	**-10.74 [-16.53, -4.96]**

* See text for limitations of the meta-analysis
CI: confidence interval; PANSS: Positive and Negative Syndrome Scale
Source: Reference 6

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continued

Clinical Point

A pharmacodynamic interaction between lamotrigine and clozapine might explain the greater effect compared with other antipsychotics

Adjunctive lamotrigine

Clinical Point

Lamotrigine might be more effective in treatment-resistant patients should this subgroup have greater glutamatergic dysfunction

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Related Resources

- Lamotrigine prescribing information and patient handout. www.lamictal.com/bipolar/hcp/prescibing_information.html.
- Augmentation strategies for schizophrenia. IPAP Schizophrenia algorithm flowchart (online interactive version), node 11. www.ipap.org/algorithms.php.

Drug Brand Names

Carbamazepine • Carbatrol, Equetro, Tegretol
Clozapine • Clozaril
Divalproex • Depakote
Ketamine • Ketalar
Lamotrigine • Lamictal
Olanzapine • Zyprexa
Risperidone • Risperdal
Valproate • Depacon, Depakene

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Bottom Line

A meta-analysis of data from 5 controlled trials supports adding lamotrigine for treatment-resistant schizophrenia patients taking clozapine but not other antipsychotics. Lamotrigine's mechanism of action and relatively safe side-effect profile may justify its use as an adjunct for targeting residual negative and cognitive symptoms in stable outpatients with schizophrenia, although evidence in this population is limited. Add lamotrigine slowly, and monitor patients closely for side effects, including rash and worsening of positive symptoms.