Attenuation of the Neuropsychiatric Effects of Ketamine With Lamotrigine

Support for Hyperglutamatergic Effects of N-methyl-D-aspartate Receptor Antagonists

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Background: The cognitive, behavioral, and mood effects of N-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine and ketamine, have been used to study the effects of NMDA receptor dysfunction. Pharmacological modulation of the effects of NMDA receptor antagonists, such as ketamine, may lead to development of novel therapeutic agents for psychiatric illnesses such as schizophrenia. Preclinical studies indicate that some ketamine effects may be mediated through increased glutamate release. In this study, we tested the hypothesis that lamotrigine, a drug reported to inhibit glutamate release, will reduce the neuropsychiatric effects of ketamine in humans.

Method: Healthy subjects (n = 16) completed 4 test days involving the administration of lamotrigine, 300 mg by mouth, or placebo 2 hours prior to administration of ketamine (0.26 mg/kg by intravenous bolus and 0.65 mg/kg per hour by intravenous infusion) or placebo in a randomized order under double-blind conditions. Behavioral and cognitive assessments were performed at baseline and after administration of the medications.

Results: Lamotrigine significantly decreased ketamine-induced perceptual abnormalities as assessed by the Clinician-Administered Dissociative States Scale (P <.001); positive symptoms of schizophrenia as assessed by the Brief Psychiatric Rating Scale positive symptoms subscale (P <.001); negative symptoms as assessed by the Brief Psychiatric Rating Scale negative symptoms subscale (P <.05); and learning and memory impairment as assessed by the Hopkins Verbal Learning Test (P <.05). However, lamotrigine increased the immediate mood-elevating effects of ketamine (P <.05).

Conclusions: Glutamate release–inhibiting drugs may reduce the hyperglutamatergic consequences of NMDA receptor dysfunction implicated in the pathophysiological processes of neuropsychiatric illnesses such as schizophrenia. Further study is needed.
SUBJECTS AND METHODS

SUBJECTS

Healthy human subjects were recruited by advertisement and were paid for their participation. Healthy subjects were selected for participation after written informed consent was obtained and following a 2-step process to exclude individuals with a past or present psychiatric illness or substance abuse disorder. The first step involved administration of the Structured Clinical Interview for DSM-IV (nonpatient version) to rule out any present or past psychiatric or substance abuse history, supplemented by a clinical interview that further evaluated personal and family history. The second step was a telephone or personal interview with an individual identified by the subject to confirm the information given by the subject. Subjects also underwent a full physical examination, blood tests, and electrocardiogram to rule out any significant medical condition. The subject’s vital signs were monitored throughout the study. Based on the above assessment, subjects were excluded who gave evidence of a current or past psychiatric or substance abuse disorder, history of clinical consultation for an emotional difficulty, significant psychiatric illness in a first-degree relative, or significant physical illness or laboratory test abnormality. Subjects were instructed to abstain from consuming psychoactive substances for 4 weeks prior to testing. Urine toxicology screens at initial screenings and on test days provided additional confirmatory evidence. Nineteen subjects agreed to participate in the study, 16 of whom completed the study. One subject developed nausea on the first test day and dropped out, 1 moved out of state, and 1 was excluded because of an inability to reliably follow instructions for behavioral testing.

Recent findings indicate that neuropsychiatric effects of NMDA antagonists may be mediated via increased glutamate release.\(^{19,20}\) NMDA receptor antagonism by phencyclidine and ketamine has been shown to increase glutamatergic neurotransmission via non-NMDA receptors (eg, the \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid and kainate receptors).\(^{13,19}\) Moghaddam and Adams\(^{13}\) have recently reported that agents that decrease glutamate release, such as the metabotropic glutamate type II receptor agonist (+)-2-aminobicyclo-(3.1.0)-hexane-2,6,25-dicarboxylate monohydrate (LY354740), can decrease motor and cognitive effects of phencyclidine in rats. Farber and colleagues\(^{19}\) have hypothesized that decreased functioning of NMDA receptors leads to cessation of drive onto GABA-ergic neurons, which cease inhibiting excitatory transmitters in the brain. These disinhibited excitatory transmitters could then act in concert to slowly hyperstimulate neurons in corticobulbar brain regions, leading to symptoms of schizophrenia. Excessive release of glutamate can lead to an increase in Na\(^+\) and Ca\(^{2+}\) influx into postsynaptic neurons (leading to toxic effects and cell death),\(^{21}\) and may be responsible for the neurodegenerative changes seen in schizophrenia.\(^{20}\)

Therefore, pharmacological agents that decrease glutamate release may be useful in the treatment of schizophrenia. Glutamate release can be inhibited by Na\(^+\)-channel blockers,\(^{22}\) Ca\(^{2+}\)-channel blockers,\(^{23}\) K\(^+\)-decreasing agents,\(^{24}\) toxins that prevent fusion of vesicles with the presynaptic membrane,\(^{25}\) and presynaptic metabotropic glutamate receptor agonists.\(^{26}\)

Several compounds that decrease glutamate release by different mechanisms are now being developed for use in humans. Lamotrigine (3,5-diamino-6-[2,3-dichlorophenyl]-1,2,4-triazine) is a new anticonvulsant that stabilizes neuronal membranes and attenuates cortical glutamate release via inhibition of use-dependent sodium channels\(^{22,27}\) and P-type and N-type calcium channels,\(^{28}\) and via its effects on K\(^+\) channels.\(^{29}\) Lamotrigine is also being investigated as an agent that may decrease excitatory amino acid (EAA)–mediated neuronal degeneration in neurological illnesses such as stroke, Parkinson disease, Alzheimer disease, and amyotrophic lateral sclerosis.\(^{21,29-31}\)

In this study, we investigated the hypothesis that pretreatment with lamotrigine would attenuate glutamate release and thereby decrease the neuropsychiatric effects of subanesthetic doses of ketamine.

PROCEDURE

The subjects completed 4 test days (active lamotrigine/active ketamine; placebo lamotrigine/active ketamine; active lamotrigine/placebo ketamine; and placebo lamotrigine/placebo ketamine) in a randomized and balanced order under double-blind conditions. The test days were spaced 3 to 7 days apart. The subjects received lamotrigine, 300 mg by mouth, or a matched placebo 2 hours before they were administered ketamine hydrochloride (Parke-Davis, Kalamazoo, Mich). Ketamine hydrochloride was administered as a 1-minute intravenous bolus of 0.26 mg/kg, followed by a 90-minute infusion of 0.65 mg/kg or saline (0.9% sodium chloride). Lamotrigine was administered 2 hours before ketamine, as lamotrigine levels have been shown to peak at 1 to 4 hours after oral administration (mean, 2 hours).\(^{31}\) Lamotrigine and ketamine levels were measured at 30 and 60 minutes after the start of ketamine infusion.

Long-term administration of lamotrigine has been associated with a rash. However, single doses of the drug have not been associated with rash.\(^{31}\) In this study, none of the subjects developed a rash.

BEHAVIORAL MEASURES

Behavioral instruments were administered at baseline and periodically after administration of lamotrigine and ketamine. The point that ketamine infusion was started was designated as the “0” time point.

Psychiatric symptoms induced by ketamine were assessed using the Brief Psychiatric Rating Scale (BPRS).\(^{7,34}\) Four key BPRS items were selected as an index of the positive symptoms of schizophrenia, based on previous reports indicating their utility and validity.\(^{35}\) and their inclusion within the empirically derived thought-disorder factor of the BPRS.\(^{33}\) These 4 key positive symptoms were

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conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content.

Three key BPRS items (blunted affect, emotional withdrawal, and motor retardation) were selected as measures of the negative symptoms of schizophrenia and their inclusion within the empirically derived withdrawal-retardation factor of the BPRS. The BPRS was administered at −150, −120, −60, −30, 5, 30, 60, 80, 120, and 180 minutes.

Mood elevation was assessed specifically with Item 1 (mood elevation) of the Young Mania Rating Scale. The Young Mania Rating Scale was administered at −150, −120, −60, −30, 5, 30, 60, 80, 120, and 180 minutes.

Dissociative effects of ketamine were measured using the Clinician-Administered Dissociative States Scale (CADSS), an instrument measuring perceptual alterations. The scale involves 19 self-report questions and 8 observer ratings scored from 0 (not at all) to 4 (extremely). The CADSS measures impairment in body perception, environmental perception, time perception, memory impairment, and feelings of unreality. These perceptual abnormalities are frequently seen in schizophrenia, particularly in the prodromal and early stages of the illness. The CADSS has been validated in healthy subjects, schizophrenic subjects, and patients with posttraumatic stress disorder. The CADSS was administered at −150, −60, 5, 80, 120, and 150 minutes.

COGNITIVE MEASURES

Ketamine-induced memory disturbance was measured with the Hopkins Verbal Learning Test (HVLT). The HVLT is designed for repeated testing of verbal memory in a short period. Different but equivalent versions of the test were administered on the 4 different days. This test consisted of 3 trials of free recall of a 12-item, semantically categorized list, followed by testing of delayed recall after 30 minutes. The HVLT was administered at 5 minutes.

RESULTS

For 16 subjects included in the analysis, the age of subjects was 34 ± 12 years and weight was 71 ± 15 kg (all values presented are mean ± SD). Eight were women (age, 32 ± 12 years; weight, 62 ± 9 kg) and 8 were men (age, 35 ± 12 years; weight, 80 ± 12 kg). Ten were white, 2 were African American, 3 were Asian, and 1 was Hispanic. Seven subjects received active lamotrigine/active ketamine before they received placebo lamotrigine/active ketamine and 9 received placebo lamotrigine/active ketamine before they received active lamotrigine/active ketamine. Ketamine levels on the active lamotrigine/active ketamine test day (30 minutes, 133 ± 55 ng/mL, and 60 minutes, 154 ± 33 ng/mL) and on the placebo lamotrigine/active ketamine test day (30 minutes, 137 ± 54 ng/mL, and 60 minutes, 158 ± 51 ng/mL) were not significantly different (Figure 1). Lamotrigine levels on the active lamotrigine/active ketamine test day (30 minutes, 3.7 ± 0.5 ng/mL, and 60 minutes, 3.6 ± 0.5 ng/mL) and lamotrigine/placebo test day (30 minutes, 3.9 ± 0.7 ng/mL, and 60 minutes, 3.9 ± 1.0 ng/mL) were also not significantly different.

BIOCHEMICAL MEASURES

Plasma ketamine levels were determined by gas chromatography/mass spectrometry with methods detailed previously. The precision of this assay was found to have coefficients of variation ranging from 3.7% and 4.9%. Lamotrigine levels were measured using commercially available radioimmunoassay kits from Smith-Kline Beecham Laboratories, Philadelphia, Pa.

DATA ANALYSIS

Data were analyzed using a random-effects model with the SAS MIXED procedure. In the random-effects model, the within-subject covariance matrix was assumed to be autoregressive. The overall ketamine effect (ketamine vs placebo); lamotrigine effect (lamotrigine vs placebo); and lamotrigine-induced modulation of the effects of ketamine were evaluated by fixed-effects ketamine × time, lamotrigine × time, and ketamine × lamotrigine × time, respectively.

All reported F test results are from mixed models. Examination of age, weight, sex, ketamine level, and order effect showed no significant associations with any outcome variables; therefore, these effects were removed from the mixed models, so as not to overparameterize them.

When the ketamine × lamotrigine × time interaction was significantly different from 0, lamotrigine modulation of ketamine effects was evaluated at each posttreatment time point separately on a post hoc basis using Bonferroni criteria. The post hoc Dunnett criteria were used to compare multiple postbaseline time points with a single baseline measure. For the outcome variables with x number of posttreatment measurements, the F value reported at each posttreatment time point is the testwise F value multiplied by the number of multiple comparisons. A postcorrection of α = .05 was used for level of significance. All tests used are 2-sided.

CADSS SCORE

No significant changes from baseline were found on the placebo/placebo day (F1,135 = 1.00; P = .33) (Figure 2). Ketamine induced a significant increase in dissociative symptoms as measured by the CADSS (ketamine × time: F5,311 = 101; P < .001). No significant lamotrigine-induced increase in dissociative symptoms was found (lamotrigine × time: F5,311 = 0.001; P > .99).

Lamotrigine led to a significant decrease in ketamine-induced dissociative symptoms (ketamine × lamotrigine × time: F9,311 = 7.63; P < .001). The postbaseline time point-wise analysis showed that lamotrigine led to a significant decrease in ketamine-induced dissociative symptoms at 5 minutes (12.0 vs 21.5; P < .001) and at 80 minutes (3.4 vs 9.1; P < .05).

BPRS POSITIVE SYMPTOM SCORE

No significant changes from baseline were found on the placebo/placebo test day (F9,135 = 0.98; P = .43) (Figure 3). Ketamine induced a significant increase in positive symptoms (ketamine × time: F9,615 = 58.02; P < .001). No significant lamotrigine-induced increase in
positive symptoms was found (lamotrigine × time: \( F_{10,610} = 0.00; P > .99 \)), and lamotrigine led to a significant decrease in ketamine-induced positive symptom score (ketamine × lamotrigine × time: \( F_{10,610} = 3.29; P < .001 \)). Lamotrigine led to a significant decrease in ketamine-induced positive symptoms at 5 (6.9 vs 8.4; \( P < .05 \)); 30 (5.7 vs 7.1; \( P < .05 \)); and 60 (5.4 vs 6.5; \( P < .05 \)) minutes but not at other time points.

**BPRS NEGATIVE SYMPTOM SCORE**

No significant changes from baseline were found on the placebo/placebo test day (\( F_{9,135} = 0.98; P = .45 \)) (Figure 4). Ketamine induced a significant increase in negative symptoms (ketamine × time: \( F_{10,610} = 3.51; P < .001 \)). No significant lamotrigine-induced increase in negative symptoms was found (ketamine × lamotrigine × time: \( F_{10,610} = 0.16; P > .99 \)). Lamotrigine led to a significant decrease in ketamine-induced negative symptoms (lamotrigine × time: \( F_{10,610} = 2.30; P < .05 \)). The time pointwise analysis showed that lamotrigine led to a significant decrease in ketamine-induced negative symptoms at 30 (6.2 vs 8.4; \( P < .05 \)); 60 (5.5 vs 8.2; \( P < .01 \)); 80 (5 vs 7.5; \( P < .01 \));
and 120 (3.6 vs 5.2; P < .01) minutes but not at other time points.

MOOD ELEVATION

For the mood elevation item of the Young Mania Rating Scale, no changes from baseline were found on the placebo/placebo test day (Figure 5). Ketamine induced a significant increase in mood elevation (ketamine × time: F3,305 = 12.58; P < .001). No significant lamotrigine-induced increase in mood elevation was found (lamotrigine × time: F3,305 = 0.06; P > .99). Immediately after administration of ketamine (at 5 minutes), lamotrigine increased ketamine-induced mood elevation (1.33 vs 0.71; ketamine × lamotrigine × time: t4 = 2.72; P < .05).

HOPKINS VERBAL LEARNING TEST

Ketamine induced significant impairments in learning a word list at the first (ketamine × time: F1,45 = 29.71; P < .001); second (ketamine × time: F1,45 = 111; P < .001); and third (ketamine × time: F1,45 = 131; P < .001) trials of the HVLT (Figure 6). Ketamine also impaired correct delayed recall of the list at 30 minutes (ketamine × time: F1,45 = 99; P < .001).

No significant effect of lamotrigine alone was found on any of the above measures. There was no significant lamotrigine-induced modulation of HVLT scores at the first trial to learn a list of words. However, lamotrigine significantly decreased impairment of learning the word list at trial 2 (ketamine × lamotrigine × time: F1,45 = 6; P < .05) and at trial 3 (ketamine × lamotrigine × time: F1,45 = 6.5; P < .05). There was a trend toward decreased impairment of delayed recall (ketamine × lamotrigine × time: F1,45 = 3.7; P = .06).

The results of this study suggest that in healthy subjects lamotrigine is able to decrease ketamine-induced symptoms resembling positive and negative symptoms of schizophrenia, perceptual alterations, and impairments in learning and memory. In contrast, lamotrigine increased the immediate mood-elevating effects of ketamine. These results are consistent with the hypothesis that, as ketamine-induced effects may be mediated by increased glutamate neurotransmission via non-NMDA receptors, lamotrigine would decrease the effects of ketamine. These results are supported by preclinical studies that have shown that group II metabotropic receptor agonists (such as LY354740) that decrease glutamate release are able to decrease the motor and cognitive effects of the NMDA receptor antagonist phencyclidine.13

The robust decrease in ketamine effects by lamotrigine is particularly striking because, as noted above, pharmacological agents acting on the dopamine receptors (haloperidol and fluphenazine) 15 (A. Malhotra, MD, unpublished data), GABA receptors (lorazepam), 14 and dopamine and serotonin receptors (clozapine and olanzapine) 16,17 have not been found to have such an attenuating effect on the full spectrum of neuropsychiatric symptoms. It is possible that higher doses of these agents led to attenuation of ketamine effects.14,16 However, at high doses, the sedative effect of these agents makes it difficult to measure the attenuating effect on ketamine-induced symptoms. In contrast, in this study, lamotrigine alone did
not have sedative effects but had a significant attenuating effect on ketamine-induced symptoms.

Effects of long-term administration of antipsychotic agents may be different from their short-term effects. Long-term administration of clozapine to schizophrenic subjects has been reported to decrease ketamine-induced positive symptoms associated with ketamine effects.\(^{18}\) It has been suggested that NMDA receptor function may be involved in the antipsychotic efficacy of long-term clozapine therapy.\(^{18}\)

A limitation of this study is that lamotrigine has also been reported to affect other neurotransmitter systems (eg, serotonin, GABA, and dopamine).\(^{43,47}\) However, lamotrigine is much less potent in this regard compared with its effect on glutamate release.\(^{27}\) It is unclear whether effects on other neurotransmitter systems are direct effects of lamotrigine or are secondary to its effects on glutamate release. It is also not known whether the effects seen in vitro with high doses of lamotrigine are applicable to clinically used doses of the drugs. However, to further specify that a decrease in glutamate release leads to decrease in effects of ketamine, this experiment will need to be repeated with more specific glutamate-release inhibitors.

An interesting finding of this study was that lamotrigine increased ketamine-induced mood elevation immediately after ketamine infusion was started, but that it decreased positive and negative symptoms. Mood elevation with ketamine has been reported previously.\(^{7,48}\) It is possible that the decrease in psychotomimetic and dissociative symptoms may have made subjects more aware of the mood-elevating effects of ketamine. Another possibility is that stimulation of non-NMDA glutamate receptors may decrease the euphoricigenic effects of ketamine, which are counteracted by lamotrigine. This observation needs further investigation.

A steady state of ketamine levels was not achieved by the bolus-infusion method used in this study; ketamine levels rose with time. In spite of that, there was a gradual decrease in ketamine effect with time. The mechanism of development of tolerance to ketamine effects is not known. It is possible that with time the subjects became more used to ketamine effects and therefore reported fewer symptoms later on in the study. An adaptive down-regulation of postsynaptic receptors is another possibility.

As mentioned above, different pharmacological agents can reduce glutamate release by different mechanisms (eg, by effects on Na\(^+\), Ca\(^+\), and K\(^+\) channels; electrical signal flow; or presynaptic autoreceptors).\(^{49}\) Lamotrigine is most potent in inhibiting the glutamate-releasing effect of the sodium channel–openver trerain, but is ineffective against potassium-induced glutamate release.\(^{27,49}\) LY354740 does not affect basal glutamate efflux but normalizes depolarization-induced activation of glutamate release;\(^{26}\) while carbamazepine also decreases veratrin-induced glutamate release but differs from lamotrigine in its anticonvulsant and behavioral effects.\(^{33,30}\) Therefore, different types of glutamate-release inhibitors need to be tested for efficacy of glutamate inhibition to reduce neuropsychiatric effects of NMDA receptor antagonists.

In this study and other studies, lamotrigine alone has not been found to produce any significant behavioral or cognitive effects.\(^{33,31}\) Subjects were unable to distinguish active and placebo lamotrigine test days. Minimal adverse effects of presynaptic glutamate-release inhibitors makes them more useful than EAA receptor antagonists for the purpose of decreasing glutamatergic transmission. The therapeutic use of NMDA and \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor antagonists has been limited because of significant behavioral and cognitive adverse effects.\(^{12,30}\)

The potential to decrease positive symptoms and, at the same time, decrease negative symptoms and elevate mood suggests that lamotrigine-like drugs may be particularly useful in the treatment of schizophrenia. We are at present conducting preliminary trials of lamotrigine as an adjunctive medication for the treatment of schizophrenia. Preliminary reports indicate that lamotrigine may be useful in the treatment of schizoaffective disorder.\(^{52}\)

Excitatory amino acid–induced neurotoxic effects have been implicated in a number of neurodegenerative disorders.\(^{23}\) If schizophrenia is conceptualized as an EAA-induced neurodegenerative disorder that starts early in life,\(^{3}\) it follows that glutamate-release inhibitors, such as lamotrigine, may be particularly useful in the early and prodromal phases of this illness (ie, they may be useful in preventing the progression of the disease).

Abnormalities of EAA neurotransmission have also been implicated in other psychiatric illnesses, such as depression, dementia, and substance abuse disorders. In this study, lamotrigine, a glutamate-release inhibitor, potentiated the mood-elevating effects of the NMDA antagonist ketamine. This suggests that decrease in EAA neurotransmission is associated with mood elevation. Lamotrigine has been reported to be useful for the treatment of bipolar depression.\(^{53}\) In this study, single short-term doses of lamotrigine were not associated with mood elevation. However, long-term inhibition of glutamate transmission with long-term treatment with lamotrigine may lead to mood elevation. The effect of glutamate-release inhibitors and NMDA and non-NMDA receptor antagonists needs to be further studied to clarify the role of EAA neurotransmission in mood disorders.

Ketamine has been shown to impair verbal memory in several studies.\(^{6,8}\) Lamotrigine led to a decrease in ketamine-induced learning and memory impairment. This suggests that decreasing glutamate release might be useful in cognitive disorders such as schizophrenia and dementia. Olney and colleagues\(^{4}\) have hypothesized that glutamate-induced excitotoxic effects may lead to widespread neuronal degeneration, such as that seen in Alzheimer disease. Preliminary reports suggest some efficacy of lamotrigine in the treatment of Alzheimer disease.\(^{31}\)

In conclusion, modulation of the EAA system with agents such as lamotrigine that decrease glutamate release may provide a novel basis for the treatment and prevention of schizophrenia and other neuropsychiatric disorders in which NMDA receptor dysfunction has been implicated.

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REFERENCES