Published in final edited form as:

J Psychiatr Res. 2017 March ; 86: 55–57. doi:10.1016/j.jpsychires.2016.10.023.

Case series: Antidepressant effects of low-affinity and low-trapping NMDA receptor antagonists did not predict response to ketamine in seven subjects

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Keywords

Antidepressant; Depression; Glutamate; NMDA receptor antagonist; Ketamine; Memantine

Letter to the Editor

Ketamine's antidepressant effects have variously been attributed to its wide-acting N-methyl-D-aspartate (NMDA) antagonism, its high-affinity for the NMDA receptor (Sanacora et al., 2008), and its trapping mechanism of blockade (Autry et al., 2011; Duman et al., 2016; Zarate et al., 2013). Several novel agents are being developed and tested that attempt to maintain ketamine's antidepressant efficacy while minimizing its side effects, particularly its psychotomimetic properties and abuse potential. Alternate NMDA receptor antagonists undergoing testing for use in mood disorders are characterized by lower NMDA receptor affinity, lower trapping, increased selectivity, and less overt receptor antagonism; the latter characteristic is linked to lower risk of dissociative and psychotomimetic effects.

Notably, a recent study called into question whether NMDA receptor inhibition is the primary mechanism of ketamine's antidepressant action (Zanos et al., 2016). The study found that the metabolic breakdown of (*R,S*)-ketamine is essential for its antidepressant effects in mice, and that (*2S,6S*) and (*2R,6R*)-hydroxynorketamine (HNK) independently

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Conflict of interest

All other authors have no conflict of interest to disclose, financial or otherwise.

Author contributions

LL: helped conceptualize study design; assisted in interpreting the statistical analysis; drafted the manuscript; edited the manuscript for intellectual content; and approved the final manuscript before submission.

DAL: helped conceptualize study design; assisted in the statistical design, analysis, and interpretation; edited the manuscript for intellectual content; and approved the final manuscript before submission.

LP: assisted in interpreting the statistical analysis; edited the manuscript for intellectual content; and approved the final manuscript before submission.

IH: assisted in drafting the manuscript; edited the manuscript for intellectual content; and approved the final manuscript before submission.

CAZ: provided research supervision; assisted in conceptualizing the study design; assisted in interpreting the statistical analysis; edited the manuscript for intellectual content; and approved the final manuscript before submission.

exert antidepressant actions that do not require NMDA receptor inhibition; furthermore, these effects appear to occur via early and sustained activation of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.

In light of this recent evidence, it should be noted that both a recent meta-analysis and an accompanying editorial emphasized that the non-ketamine NMDA receptor antagonists do not appear to have the same robust, rapid, and relatively sustained antidepressant properties as ketamine (Kishimoto et al., 2016; Sanacora, 2016). To date, no controlled trials comparing ketamine versus non-ketamine NMDA receptor antagonists have been conducted, though such trials would be key to identifying characteristics of the shared treatment response across NMDA receptor antagonists. Here we present a case series of subjects treated with both ketamine and a non-ketamine NMDA receptor antagonist.

Our laboratory previously investigated the putative antidepressant effects of two NMDA channel blockers with mechanisms of action that differ from those of ketamine. A double-blind, placebo-controlled, crossover trial of a single infusion of AZD6765—a low-trapping NMDA channel blocker—found that this agent had short-lived and very modest antidepressant effects (Zarate et al., 2013) (NCT00986479). Another double-blind, placebo-controlled, parallel study found that daily oral doses of memantine monotherapy (5–20 mg/day) were not effective in treating major depressive disorder (MDD) (Zarate et al., 2006) (NCT00040261); memantine is a low-affinity, uncompetitive, open-channel NMDA receptor antagonist. Seven subjects who had received active study drug in one of these two studies subsequently participated in one of a series of different ketamine studies (NCT00088699) (Ibrahim et al., 2012). In all ketamine studies, subjects received the same dose of ketamine: a single 0.5 mg/kg infusion administered over 40 mins. Four of the seven subjects were enrolled in the AZD6765 trial and three were enrolled in the memantine trial. All but one of the seven subjects (AZD6765-A; Fig. 1) received their study drug before receiving ketamine.

For each of these studies, all subjects were inpatients at the National Institute of Mental Health (NIMH) Mood Disorders Research Unit in Bethesda, Maryland. Inclusion and exclusion criteria have been previously described (Ibrahim et al., 2012; Zarate et al., 2006; Zarate et al., 2013). All subjects gave written informed consent.

For six of the seven subjects, depressive symptom severity was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS), but the Hamilton Depression Rating Scale (HAM-D) was used in one subject (AZD6765-A). To examine the percent change in score from baseline to post-treatment, the best response to the non-ketamine NMDA receptor antagonist—regardless of when it occurred after 230 mins—was compared to the best response to ketamine, regardless of when it occurred; these two values often occurred at different time points. Response was defined as > 50% reduction in baseline score, partial response as a 25–50% decrease in baseline score, and non-response as a <25% reduction or an increase in score from baseline.

The seven subjects (4M, 3F) ranged in age from 42 to 63 years (mean 53.4 ± 7.7) at their first trial and 42 to 64 years (mean 58 ± 7.7) at their second trial (mean duration of illness: 33.2 ± 16.5 years). Patients reported psychotomimetic and dissociative side effects with

ketamine, but none reported similar effects with the non-ketamine NMDA receptor antagonists.

We examined change in each subject's depression rating scale score from placebo or from baseline to active drug (for both ketamine and the other NMDA receptor antagonist). Only three subjects received placebo (during the AZD6765 trial), and these showed no antidepressant response (mean improvement: 13.9%). In four patients receiving AZD6765, there was a 38.0% reduction in depression score (range: 9.1%–92.3%). For the three patients who received memantine, a mean 4% reduction in MADRS score was observed (range: 17.6% improvement to 6.9% worsening from base-line). Overall, drug response to the non-ketamine NMDA receptor antagonist ranged from 92.3% improvement to 6.9% worsening, with a mean 23.6% improvement. Of the seven subjects, one achieved full response, one achieved partial response, and five were non-responders.

When these subjects received ketamine, antidepressant response ranged from 84% improvement to 7% worsening, with a mean improvement of 47.8%. Three subjects achieved full response, two achieved partial response, and two were non-responders. Thus, five of seven subjects experienced either a partial or full response to ketamine versus only two of the same seven subjects receiving a different NMDA receptor antagonist.

Of the two subjects who responded to the NMDA receptor antagonist, one (AZD6765-A) experienced robust improvement in response to both ketamine and AZD6765 but never received placebo because his antidepressant response endured, thus not permitting crossover to the other condition. The second subject (AZD6765-D) had a partial response to AZD6765 but did not respond to ketamine.

In summary, in these subjects, the antidepressant effects of the low-trapping NMDA receptor antagonist AZD6765 and those of the low-affinity NMDA receptor antagonist memantine did not correlate with those of ketamine. That is, response to the non-ketamine NMDA receptor antagonists in no way predicted response to ketamine. Despite the small sample size and the case series nature of the study, the results provide additional evidence for the possibility that ketamine's antidepressant effects are not primarily mediated via NMDA receptor antagonism.

Acknowledgments

The authors thank the 7SE research unit and staff for their support.

Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; ZIA MH002857; NCT00986479, NCT00040261, NCT00088699), by a NARSAD Independent Investigator Award to Dr. Zarate, and by a Brain and Behavior Mood Disorders Research Award to Dr. Zarate. Dr. Zarate is listed as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (2*S*)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (2*R*,6*S*)-ketamine metabolites in the treatment of depression and neuropathic pain. Dr. Zarate is listed as co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorders; he has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government.

Role of funding source

The NIMH, NARSAD, and the Brain and Behavior Research Foundation had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

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Fig. 1.

Each line represents one subject and each point represents that subject's maximum percent change in Montgomery-Asberg Depression Rating Scale (MADRS) from baseline anytime at or after 230 mins. Percent change in score for subject AZD6765-A reflects Hamilton Depression Rating Scale (HAM-D) score rather than MADRS score.