Rapid-Acting Glutamatergic Antidepressants: The Path to Ketamine and Beyond

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Traditional antidepressants require many weeks to reveal their therapeutic effects. However, the widely replicated observation that a single subanesthetic dose of the N-methyl-D-aspartate glutamate receptor antagonist ketamine produced meaningful clinical improvement within hours, suggested that rapid-acting antidepressants might be possible. The ketamine studies stimulated a new generation of basic antidepressant research that identified new neural signaling mechanisms in antidepressant response and provided a conceptual framework linking a group of novel antidepressant mechanisms. This article presents the path that led to the testing of ketamine, considers its promise as an antidepressant, and reviews novel treatment mechanisms that are emerging from this line of research.

Key Words: Antidepressants, glutamate, ketamine, rapid-acting, review, treatment mechanisms

The field of antidepressant research has had little success in developing fundamentally novel antidepressant mechanisms, leaving psychiatrists with relatively few pharmacologic options for the treatment of patients with depression. Available treatments primarily block monoamine transporters, monoamine receptors, or the activity of monoamine oxidase (1). The emergence of serotonin reuptake inhibitors (SRI) revolutionized the treatment of depression by providing physicians with safe and easily prescribed medications. The SRIs were well suited to prescription by primary care physicians, bringing effective pharmacotherapy for depression to patients who obtained prescription by primary care physicians, bringing effective pharmacotherapy for depression to patients who obtained psychiatric treatment in this way (2). Despite becoming a “Prozac Nation,” the limited effectiveness of pharmacotherapies for depression has been discouraging (3,4). Major depression remains a leading cause of disability in the world (5). Furthermore, the National Institute of Mental Health STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study found that only 27% of patients did not achieve remission despite trials of four antidepressant medications, and that the primary or adjunctive medication selected for treatment made little difference (6). In addition, the average time to reach remission for the treatment-responsive subgroup of patients was 7 weeks. Thus, there is a tremendous need for new antidepressant treatment mechanisms and, particularly, for mechanisms that might reduce the onset of antidepressant efficacy.

This review describes the path that led to the testing of ketamine as a rapid-acting antidepressant, alterations in glutamate neurotransmission in depression that might be targeted by ketamine, and recent insights into the mechanisms underlying the antidepressant effects of ketamine and other novel treatment strategies. This evolving story has been summarized in previous reviews, and the reader is referred to these reports for additional detail (7–9).

N-Methyl-D-Aspartate Receptor Antagonists as Rapid-Acting Antidepressants

The testing of glutamatergic drugs for the treatment of depression has a surprisingly long history. In 1959, Dr. George Crane reported on the effects of a tuberculosis antibiotic that was known to cause seizures and exacerbate psychosis, D-cycloserine. In his first case series, he found that D-cycloserine produced mood improvement in 30 of 37 tuberculosis patients suffering from depression, predominately within 2 weeks (10). When he replicated these findings in another case series, he concluded, “It is difficult to explain why psychiatric benefits should have occurred almost immediately following drug administration” (11). More than 50 years later, the first placebo-controlled replication of this finding reported progressive improvement with D-cycloserine over 6 weeks of treatment (12). D-cycloserine is a partial agonist at the glycine _B_ coagonist site of N-methyl-D-aspartate (NMDA) glutamate receptors bearing the GluN2A and GluN2B subunits (previously NR2A and NR2B subunits) and a full agonist of NMDA receptors containing the GluN2C and GluN2D subunits (13,14). In light of the antidepressant efficacy of NMDA receptor antagonists, D-cycloserine may have reduced symptoms of depression by attenuating the function of NMDA receptors bearing GluN2A or GluN2B subunits. However, it is not yet clear whether the agonist or antagonist features of D-cycloserine account for its antidepressant efficacy.

The next glutamatergic agent studied was amantadine, which was studied for depression before its mechanism of action was identified. By the late 1960s, amantadine was deemed helpful for treating Parkinson disease, a condition commonly associated with depression. For this reason, it was tested in a pilot study that produced encouraging beneficial effects (15). Amantadine and memantine were demonstrated subsequently to be low- and moderate-affinity NMDA receptor antagonists, respectively (16). However, when administered at 20 mg per day, memantine failed in its initial placebo-controlled trial (17). Subsequent memantine studies have not yielded definitive results but suggest adjunctive memantine merits further study in bipolar depression (18,19), perhaps at doses up to 40 mg per day (20). More recently, another low-affinity NMDA receptor antagonist, AZD6765, showed promising antidepressant effects in humans at doses that do not produce psychosis (21).

Following early clinical studies, preclinical models revealed the antidepressant potential of glutamatergic agents (22,23); see also...
the review by Pilc et al. in this issue). Building on the observation that inescapable stress exposure in animals attenuated long-term potentiation, an NMDA receptor-dependent process, investigators found that many types of drugs that reduce NMDA receptor function had antidepressant-like effects in several animal models of depression including a glycineB site partial agonist, a competitive NMDA receptor antagonist, an uncompetitive NMDA receptor antagonist, and a GluN2B-selective uncompetitive NMDA receptor antagonist (24–26). Reduced NMDA receptor function emerged as a correlate of long-term antidepressant administration (27,28). Thus, by the mid-1990s, there was a compelling preclinical literature that supported the earlier clinical findings suggesting that NMDA receptor antagonists had antidepressant properties, but this hypothesis had not yet had an unambiguous test in humans.

Although we were aware of the earlier literature, when we studied ketamine effects in depressed patients, we did not expect the rapid and robust antidepressant effects that emerged. In the late 1980s, we began studying ketamine effects in healthy subjects (29) to link glutamate synaptic dysfunction to schizophrenia (30). We also used ketamine to provide the first clinical evidence of enhanced NMDA receptor function associated with alcoholism risk and alcohol dependence (31). When studying ketamine effects in depressed patients, we used the ketamine dose and infusion paradigm adopted from these earlier ketamine studies to facilitate comparison of responses to ketamine in depressed patients with healthy subjects and recovering alcohol-dependent patients with the objective of characterizing alterations in NMDA receptor function related to depression.

Using this approach, we and other groups were impressed by the rapid onset of the robust antidepressant effects produced by a single dose of ketamine, producing complete remission within 24 hours in some patients (32–36). As shown in Figure 1, the antidepressant effects of ketamine were not present until after the psychotogenic and euphoric effects of ketamine had disappeared. This temporal distinction first suggested that the antidepressant effects arose as a rapid neuroadaptation to the acute effects of ketamine in the brain. Across studies reported to date (Figure 2), antidepressant effects emerge by 2 to 4 hours (36). By 24 hours, studies report substantial improvement and response of depression symptoms in approximately 50% to 80% of patients (36,37). All studies report substantial improvement and response of depression symptoms, including suicidal ideation (38,39). The clinical benefits after a single ketamine dose may last as briefly as 1 to 2 days and may last longer than 2 weeks (36).

Even at this early research stage, investigators began to explore whether subgroups of depressed patients might respond particularly well to ketamine. For example, ketamine appears effective for “treatment-resistant” patients (40), even patients who did not respond to electroconvulsive therapy (35); depressed individuals with a family history of alcoholism (41,42); and depressed patients with comorbid alcohol dependence (43). Also, because ketamine is an effective analgesic, it has been used to treat depression emerging in the context of chronic pain (44,45).

Ketamine, thus far, has shown evidence that it is safe for the treatment of depression. Ketamine has a long track record of safety when administered as a surgical anesthetic at doses far higher than needed for antidepressant treatment when administered with appropriate levels of medical screening, monitoring, and clinical follow-up (46). It is not yet clear whether this safety profile extends to settings in which patients are less well prepared and less intensively monitored and followed. A principal safety concern is whether inducing psychosis via ketamine administration is safe for depressed patients. Prospective follow-up data in healthy human subjects (47) and psychiatric patient populations including schizophrenia patients (48,49) suggest that psychotogenic doses of ketamine in research settings do not pose a clinical risk to patients. In the limited collected reports of the antidepressant effects of ketamine, the safety profile in depressed patients appears to resemble that of healthy subjects (32–35,50). A particular concern for rapid-acting antidepressants, like ketamine, is whether there is an abrupt worsening or rebound of suicidal ideation or impulses as the antidepressant effects of ketamine dissipate. So far, in the modest number of patients studied to date, this problem has not been reported. However, this important issue will need careful prospective study in larger samples. An additional concern for depressed patients who might have bipolar disorder is whether ketamine accelerates the transition to mania. This has not been a problem in the larger trials to date (34,51) or in two cases of extended treatment with ketamine (52). One case of mania attributed to ketamine infusion has been reported; however, attributions of causality related to switches in mood state in

Figure 1. The effects of intravenous ketamine .5 mg/kg and a saline placebo in patients with major depression (n = 7). In this figure, the antidepressant effects of ketamine emerge after the psychotogenic and euphoric effects of ketamine abate. The top figure presents the reduction in Hamilton Depression Scale (HDRS) scores in patients administered ketamine but not placebo. The middle figure presents the production of psychosis, as measured by a visual analog scale (VAS) of “high,” following ketamine but not saline. The bottom figure presents the production of psychosis, as measured by the Brief Psychiatric Rating Scale (BPRS) positive symptom subscale. The repeated-measures analysis of variance performed on each of these outcomes revealed highly significant ketamine by time interaction effects (p < .005). Reprinted from Berman et al. (32), with permission from Elsevier, copyright 2000.
bipolar disorder are extremely complicated, and so this important issue awaits further rigorous study (53).

The intravenous infusion paradigm used in the published antidepressant trials provides excellent control of drug exposure. This level of control facilitates the exploration of the lowest effective dose of ketamine for the treatment of depression and the margin of safety between the antidepressant and perception-altering doses of ketamine. Furthermore, it is important to evaluate rigorously whether its antidepressant effects are dose-related, that is, if maximal antidepressant effects emerge in the perceptual dose range. Nonetheless, unpleasant ketamine effects generally abate within an hour after the termination of drug administration (29,32). This property, combined with the ability to terminate infusions if unpleasant effects emerge to limit drug exposure, enables clinicians to minimize risks to patients (54). Restricting ketamine administration to clinical settings also provides a way to minimize the impact of its abuse liability (55). We are aware of one un-published case of a person with a substance abuse history who abused ketamine after receiving it intravenously for treatment-refractory depression, highlighting the importance of addressing its abuse liability within the context of treatment.

Alternatives to intravenous ketamine administration may increase access to ketamine. Case reports describe antidepressant effects associated with ketamine administered via intramuscular and oral routes (52,56,57). The antidepressant effects of intranasal ketamine are being studied (ClinicalTrials.gov: NCT01304147). If ketamine were effective in doses below the threshold for perceptual effects, then the availability of oral and intranasal ketamine could provide convenient modes of administration for treatment in ambulatory settings. The risks may be analogous to the NMDA receptor antagonist dextromethorphan. Dextromethorphan is dispensed widely as a cough suppressant despite concerns related to its abuse liability (58) and psychotogenic potential (59).

A critical obstacle to the broader study and implementation of ketamine treatment for depression is the lack of clarity as to how to sustain its antidepressant effects. Pilot studies suggest that ketamine may be sustained by repeated intermittent administration (50,60). Although the data are extremely preliminary and not placebo-controlled, with repeated ketamine dosing, the antidepressant effects may persist for longer periods in some patients. This observation may be consistent with sensitization to some ketamine effects with weekly administration in animals (61). The possible sensitization to the therapeutic effects of ketamine may contrast with the psychotogenic effects of ketamine, which do not appear to sensitize with a limited number of exposures in the laboratory (62). Also, nonresponse to initial dosing may predict poor response to repeated dosing (50,60). Thus, one advantage of the use of ketamine as an antidepressant may be the ability to predict whether a longer course of ketamine treatment is indicated after a dose or two of the drug. The maximal duration of the beneficial effects of ketamine are unknown. There are now reports of cases where repeated dosing of ketamine has treated symptoms of unipolar or bipolar depression for 6 months or more (52,63,64). However, 6 months of treatment is still far shorter than the duration of long-term antidepressant treatment for chronic major affective disorder.

One question raised by the prospect of long-term repeated dosing of NMDA receptor antagonists is whether, at some point, adverse effects that have been observed in animals or associated with ketamine abuse might emerge. In animals, repeated daily administration of NMDA receptor antagonists produce glutamatergic synaptic deficits including reduced ligand binding to NMDA receptors in frontal cortex (65), reduced gamma-aminobutyric acid (GABA) neuronal function (66), increased striatal dopamine release (67), depletion of prefrontal cortex dopamine (68), impaired cognitive function, and an amotivational state (69). Repeated ketamine administration also causes oxidative stress that contributes to loss of parvalbumin positive GABAergic interneurons (70). At doses higher than the current antidepressant dose of ketamine, it produces reversible neural injuries (71), including the expression of heat shock proteins and vacuolization (72,73).

In humans, ketamine abuse has been associated with cognitive impairments and altered thought content (74,75). Ketamine abusers also show cortical white matter deficits in a study using diffusion tensor imaging (76), cortical gray matter deficits on magnetic resonance imaging (77), and alterations in cortical functional connectivity (78). In addition, ketamine abuse may be associated with cystitis (79) and biliary dilatation (80). The findings in chronic ketamine abusers may overestimate the clinical risks of long-term treatment. Ketamine abusers often take multiple substances, administer higher ketamine doses than needed to treat depression, and administer these doses more frequently than would be needed for treatment (75). Nonetheless, the development of long-term ketamine treatment for depression would need to be accompanied by careful studies of its safety.

An alternative strategy would be to use ketamine to induce remission and then to prevent depressive relapse using other medications or psychotherapeutic approaches. Two inadequately powered studies tested this hypothesis and failed to demonstrate that riluzole extended ketamine effects (81,82). However, additional study of the protective effects of psychotherapy, antidepressants, and lithium, given their capacity to protect against relapse of depression, is justified (83–86). Because ketamine may

![Figure 2. A summary of the antidepressant effects of ketamine from seven published studies (five in unipolar major depression and two (*) in bipolar depression). The response rates are both impressive and consistent across studies. The data are collected from a total of 130 patients. Reprinted from aan het Rot et al. (36), with permission from Elsevier, copyright 2012. IV, intravenous.](http://www.sobp.org/journal)
Glutamate and the Neurobiology of Depression

Glutamatergic neurotransmission emerged over a decade ago as an extremely important area for depression research (91). This progress was inevitable as glutamate neurons are important targets for monoamine systems previously implicated in depression neurobiology and treatment, cortical neuroimaging studies in depression describe alterations in glutamatergic connectivity, and glutamatergic functional connectivity is targeted by both psychotherapeutic and neurostimulation treatments for depression (92).

To set the stage for the subsequent consideration of novel treatment mechanisms, this review briefly considers the downstream consequences of the loss of glia. A more detailed consideration of these issues is presented in another article in this issue (see Sanacora and Banasr). Glia are key regulators of glutamatergic neurotransmission because of their role in the inactivation of glutamate (93). There is robust evidence that astrocyte and satellite oligodendrocyte populations are reduced in prefrontal cortex and other cortical regions in postmortem tissue from individuals who had suffered from major depression (94) and bipolar disorder (95), consistent with the efficacy of ketamine in both unipolar and bipolar depression, as noted earlier. The glial loss in depression may reflect the convergence of many features of stress response in animal models that are also associated with episodes of major depression in humans. These factors include immunologic attack on glial integrity as a consequence of elevated brain cytokine and cortisol levels, increased levels of reactive oxygen species as a consequence of metabolic activation, and reduced levels of free radical scavengers including glutathione, and stress-induced glutamate release (96,97).

In preclinical stress models, glial loss has a number of downstream consequences that may carryover into the pathophysiology of major depression. Glial loss, produced by specific glial toxins, produces biochemical and behavioral signs of depression in animal models (98). Because glia are centrally involved in glutamate inactivation, glial loss may elevate glutamate levels in both synaptic and extrasynaptic spaces. Increased extrasynaptic glutamate levels would be expected to have additional consequences for glutamate synaptic transmission (Figure 3A). First, one might see excessive stimulation of presynaptic and extrasynaptic metabotropic glutamate receptors (mGlURs). Overstimulation of presynaptic mGlUR2 receptors has been shown to depress glutamate neurotransmission and compromise synaptic connectivity (99), consistent with the association of elevated anterior cingulate glutamate levels and reduced cingulate functional connectivity in major depression (100). Stress-induced glutamate release also may enhance an NMDA/alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) bias in signaling as stimulation of postsynaptic group I mGlURs enhances NMDA receptor signaling promotes long-term depression and internalization of AMPA receptors (101). A second consequence of elevated extrasynaptic glutamate levels is overstimulation of extrasynaptic NMDA receptors, particularly those bearing the GluN2B/NR2B subunit. Overstimulation of these receptors has a number of downstream consequences including phosphorylation of elongation factor-2 (ElF-2), suppression of cyclic adenosine monophosphate response element binding protein levels, reduction in brain-derived neurotrophic factor levels (BDNF), culminating in dendritic regression and activation of apoptotic signaling pathways (102,103). These processes contribute to loss of dendritic spines and dendritic atrophy consistently reported in animal models of stress and may contribute to neuronal atrophy and synapse loss in major depression (104). Thus, glial deficits in depression may contribute to abnormalities in cortical functional connectivity by compromising structural connectivity and dysregulating glutamate synaptic transmission.
From Glutamate Pathophysiology to Novel Therapeutics

This model of glutamate synaptic dysfunction in depression yields a number of testable hypotheses regarding the treatment of this disorder. Studies support the hypothesis that immunologic activation, perhaps mediated by glial dysfunction, contributes to the emergence of depression-like states that are responsive to the effects of NMDA receptor antagonists. For example, NMDA receptor antagonists appear to treat fatigue and dysorphic mood associated with multiple sclerosis and interferon treatment for hepatitis C infection (105,106). A component of this response to NMDA receptor antagonists may be related to their anti-inflammatory effects (107).

New pathways to antidepressant development are suggested by the two novel mechanisms underlying the antidepressant efficacy of ketamine, that is, that ketamine overcomes glutamate synaptic depression by 1) stimulating synaptic glutamate release and enhancing synaptic AMPA receptor signaling and 2) blocks extrasynaptic NMDA receptors (Figure 3B). The hypothesis that ketamine might increase synaptic release is supported by a number of observations related to the effects of NMDA receptor antagonists: 1) they reduce the activation of GABA neurons in hippocampus and prefrontal cortex, 2) they increase neuronal firing and raise extracellular glutamate levels in prefrontal cortex, and 3) they increase cortical glutamate levels and activation (30,108–110). The increase in glutamate release produced by ketamine seems to be essential for its antidepressant effects as AMPA receptor antagonists block its efficacy in animal models (111). Also, reduced glutamatergic activation appears to predict the magnitude of the antidepressant response to ketamine in humans (112). Once stimulation of AMPA receptors is restored, antidepressant effects are mediated by stimulation of signaling in the Akt/mammalian target of rapamycin pathway, resulting in a rapid sprouting of dendritic spines (87). These effects are dependent on the induction of BDNF, because the antidepressant effects of ketamine in both animals and humans are attenuated in association with the low activity Met allele of the BDNF gene (Figure 4) (113,114). This property may render BDNF genotyping an important biomarker for the clinical response to ketamine in humans. The blockade of extrasynaptic NMDA receptors also appears to be critical to the antidepressant effects of ketamine. By preventing the phosphorylation of EIP-2 and relieving inhibition of BDNF synthesis, NMDA receptor antagonists enable the regrowth of dendritic spines and contribute to antidepressant behavioral effects (103).

The first alternatives to ketamine suggested by this model are drugs that selectively block NMDA receptors bearing the GluN2B subunit. This subunit is an important component of the extrasynaptic NMDA receptors (102). Perhaps for this reason, there might be greater separation of the dose thresholds for the antidepressant and psychotogenic effects of GluN2B selective and nonselective NMDA receptor antagonists. To date, the data do not adequately test this hypothesis. For example, the GluN2Bpreferring NMDA receptor antagonist, CP 101,606 (115) had rapidly emerging antidepressant effects, but it also produced dissociative effects in 6 of 15 patients. In another study, no reports of psychosis emerged during 12 days of oral dosing of a GluN2B-prefering NMDA receptor antagonist MK-0657, but antidepressant effects during this study were limited (116).

Several treatment mechanisms predicted by their ability to reduce the consequences of excessive extrasynaptic glutamate levels show efficacy in animal models of depression. Harkening back to Crane’s early work, a number of groups have studied partial agonists at the glycineB site of the NMDA glutamate receptor including 1-aminocyclopropanecarboxylic acid (24). Glyx-13 is another promising NMDA receptor partial agonist that was initially thought to act via the glycineB site (117), although the specific site at which it acts is not settled. Other treatment mechanisms implicated by this model include mGluR2 and mGluR5 receptor antagonists. Like ketamine, mGluR2 antagonists appear to produce rapid antidepressant effects in animal models (118) that are mediated by increased glutamate release and stimulation of AMPA receptors (119). mGluR2 agonists have anxiolitic activity in animals and humans (120). Thus, if mGluR2 antagonists are developed for humans, it will be important to determine whether they have anxiogenic effects. mGluR5 receptor antagonists, known to potenti- tiate psychotogenic effects of NMDA receptor antagonists (120), also have anxiolytic and antidepressant effects in animal models (121,122). Thus, tests of the efficacy of novel mGluR2 antidepressants will need to address safety and tolerability issues. AMPA receptor potentiators or AMPAkines also would be predicted to rapid-onset antidepressant effects, consistent with their rapid “antidepressant” effects in a submission model (123), via their capacity to compensate for deficits in synaptic AMPA receptor function.

Figure 4. This figure depicts the impact of a Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene on the effects of ketamine on dendritic spine growth in rodents (A) and on improvement in depression (Hamilton Depression Scale [HAM-D] Score). (A) The left side of this figure presents the results of two-photon microscopy of labeled layer 5 pyramidal neurons in slices from the prefrontal cortex. A robust proliferation of large and long dendritic spines is observed following ketamine administration in wild-type (WT) animals. However, mice that have had the Met allele inserted into the BDNF gene (Met/Met), rendering that gene less effective, show 1) reduced dendritic spine density compared with the WT animals at baseline and 2) markedly blunted increases in dendritic spine density following administration. *p < .05, **/## p < .01; n.s., not significant. Reprinted from Liu, et al. (113), with permission from Elsevier, copyright 2012. (B) This figure presents the association of the rs6265 single nucleotide polymorphisms in the BDNF gene with clinical response to ketamine in patients with major depression. Data from LaJe et al. (114). In this group, 41 patients possessed the Val/Val genotype, 19 patients were Val/Met, and 2 patients were Met/Met. Fifty-eight patients were of European ancestry, and four patients were African American. The interaction of genotype and ketamine effects was highly significant (F = 5.59, df = 4, p = .0007).
(124) or cytokine receptor antagonists (125). Another strategy would be to try to protect glia from free radical injury by raising glial glutathione levels. For example, raising glutathione levels using N-acetylcysteine may be helpful as an adjunctive treatment strategy for bipolar depression (126). Lastly, riluzole and beta-lactam antibiotics increase the expression of glutamate transporters and show efficacy in animal models (98) (Sanacora and Banasr, this issue). Preliminary open-label data support the efficacy of riluzole in the treatment of depression (127), but larger and more rigorous studies are needed.

Discussion
Research on rapid-acting antidepressants is shaping expectations regarding what might be achieved through antidepressant treatment. Ketamine research has proved to unlock new insights into the neurobiology of depression and to point to new and otherwise unexpected classes of antidepressant medications. Fifty years of antidepressant research suggested that antidepressants needed to act on monoamine systems and that treatment required weeks to months to produce benefits in responding patients. It is now clear that significant clinical improvement in depression symptoms may occur within hours of drug administration. Furthermore, ketamine and the putative antidepressants that have followed it have clearly demonstrated that antidepressants need not produce their therapeutic effects via direct effects on monoamine receptors. Ketamine administration remains a research procedure with significant potential risks. Despite growing enthusiasm for rapid implementation, further research will be needed before it is appropriate to consider it a routine treatment for depression. Until that time, ketamine should be limited predominately to research contexts to ensure that adequate review of risks and benefits has occurred before ketamine infusion, enhance the informed consent process before ketamine infusion, protect individuals patients undergoing ketamine treatment, and increase the likelihood that the growing experience with ketamine infusion informs the field of depression research. Ketamine has proven to be a useful prototype for rapid-acting antidepressants, but there may be better alternatives to ketamine for this purpose. Nonetheless, it is a moment of tremendous excitement. Important new treatments may emerge from the research directions outlined in this article and help to address the tremendous need for depression treatments that are more effective and that relieve depression rapidly.

We gratefully acknowledge the support of the State of Connecticut Department of Mental Health and Addiction Services for its support of the Abraham Ribicoff Research Facilities of the Connecticut Mental Health Center, the Department of Veterans Affairs, via its funding of the VA National Center for PTSD, the National Institute of Mental Health (Grant Nos. MH17871, MH093897), and the National Center for Advancing Translational Science (Clinical and Translational Science Award Grant No. UL1 RR024139).

Dr. Krystal has served as a scientific consultant to the following companies (the Individual Consultant Agreements listed are less than $10,000 per year): Aisling Capital, Astellas Pharma Global Development, AstraZeneca Pharmaceuticals, Biocortech, Brintnell & Nicolini, Easton Associates, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Lundbeck Research USA, Medivation, Merz Pharmaceuticals, MK Medical Communications, F. Hoffmann-La Roche, SK Holdings, Sunovion Pharmaceuticals, Takeda Industries, and Teva Pharmaceutical Industries. He is on the Scientific Advisory Board for the following companies: Abbott Laboratories, Bristol-Myers-Squibb, Eisai, Eli Lilly, Forest Laboratories, Lohocla Research Corporation, Mmeneysine Pharmaceuticals, Naurex, Pfizer Pharmaceuticals, and Shire Pharmaceuticals. He holds more than $150 in exercisable warrant options with Tetragenex Pharmaceuticals. He is on the Board of Directors of the Coalition for Translational Research in Alcohol and Substance Use Disorders. He was the principal investigator of a multicenter study in which Janssen Research Foundation provided drug and some support to the Department of Veterans Affairs. He is editor of Biological Psychiatry (Income more than $10,000). He has the following patents and inventions: 1) Seibyl JP, Krystal JH, Charney DS. Dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia. Patent no: 5447948, 5 September 1995; 2) he is a coinventor with Dr. Gerard Sanacora on a filed patent application by Yale University related to targeting the glutamatergic system for the treatment of neuropsychiatric disorders (PCTWO06108055A1); 3) Intranasal Administration of Ketamine to Treat Depression (pending). Dr. Sanacora has received consulting fees from Abbott Laboratories, AstraZeneca, Avanier Pharmaceuticals, Bristol-Myers Squibb, Evotec, Eli Lilly & Co., Hoffman La-Roche, Novartis, and Novum Pharmaceuticals over the past 24 months. He has also received additional grant support from AstraZeneca, Bristol-Myers Squibb, Hoffman La-Roche, Merck & Co., and Sunovion Inc. over the past 24 months. In addition, he is a coinventor on a filed patent application by Yale University (No. PCTWO06108055A1). Dr. Duman reports having received honorarium fees from Lilly, Pfizer, Bristol Myers Squibb, Johnson & Johnson, Forest, and Lundbeck; consulting fees from Taisha; and research support from Lilly, Lundbeck, Johnson & Johnson, and Forest.


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