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Current Trends in Identifying Rapidly Acting Treatments for Depression

Dawn F. Ionescu, M.D.[1,3] and **George I. Papakostas, M.D.**[1,2,3]

[1]Depression Clinic and Research Program, Massachusetts General Hospital, Boston, MA, USA

[2]Clinical Trials Network and Institute, Massachusetts General Hospital, Boston, MA, USA

[3]Harvard Medical School, Boston, MA, USA

Abstract

Traditional antidepressant medications generally take weeks-to-months to achieve effect. However, the breakthrough finding of ketamine's rapidly acting antidepressant properties has inspired a decade-and-a-half of progress towards the identification of treatments that work quickly—within hours-to-days. This paradigm-shift in the discovery of antidepressant therapies has significantly changed the current landscape of antidepressant drug development. Building on this, the current review briefly highlights the recent trends in research towards identifying rapidly-acting antidepressants. Specifically, ketamine, GLYX-13, nitrous oxide, metabotropic glutamatergic receptor modulators, scopolamine, opioid-receptor modulators, and low field magnetic stimulation are discussed.

Address correspondence to: George I. Papakostas, M.D. Massachusetts General Hospital, Depression Clinical and Research Program, Clinical Trials Network and Institute, 1 Bowdoin Square, 6th Floor, Boston, MA 02114, Phone: 1-617-726-6697, Fax: 1-617-724-3028, gpapakostas@partners.org; Dawn F. Ionescu, M.D. Massachusetts General Hospital, Depression Clinical and Research Program, 1 Bowdoin Square, 6th Floor, Boston, MA 02114, Phone: 1-617-643-0491, Fax: 1-617-724-3028, dionescu@mgh.harvard.edu.

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Keywords

Depression; treatment-resistant depression; major depressive disorder; experimental therapeutics; rapid treatments; psychopharmacology; ketamine; GLYX-13; nitrous oxide; metabotropic glutamatergic receptor (mGluRs) modulators; scopolamine; kappa-opioid receptor; LFMS

Introduction

In the 1930s, amphetamine was the first drug marketed for the treatment of “mild depression.”[1] Two decades later, the serendipitous identification of the antidepressant properties of both iproniazid and imipramine[2] launched the modern era of antidepressant drug discovery. Because these medications are thought to exert their antidepressant activity through the modulation of monoamnergic neurotransmission (whether selective [3] or non-selective [4, 5]), antidepressant drug development over the past half-century has primarily focused on medications with similar mechanisms of action[2], with few exceptions involving non-monoaminergic agents.[6, 7] Without a doubt, millions of patients have benefitted from antidepressant drug revolution. However, despite tremendous strides in the treatment of depression, 30-40% of depressed patients will continue to remain depressed even with adequate antidepressant treatment trials.[8] Furthermore, even when they do work, currently approved antidepressant medications generally take weeks-to-months to have an effect. Indeed, the global burden of untreated depression is one of the highest of all diseases,[9, 10] making the discovery of rapidly-acting antidepressants a worldwide priority.

Thus far, breakthrough antidepressant medications that work within hour-to-days, rather than weeks-to-months, remain elusive. Trials that have examined the antidepressant properties of the quick-acting stimulants have been largely lacking or negative.[11, 12] Similarly, though benzodiazepine augmentation represents a potential rapid strategy for improving antidepressant activity and adherence, [13-15], *worsening* mood has also been reported.[15] Electroconvulsive therapy (ECT)—the current gold-standard treatment for depression—represents a potential exception, for it has faster antidepressant properties compared to traditional monoaminergic psychopharmacological approaches;[16, 17] in one study, more than half of the patients (54%; 136/253) experienced response by the end of the first week.[17] Despite ECT's proven antidepressant efficacy, it remains a “last resort” for many patients, given its cognitive side effects, lack of access in many areas, and continued societal stigma. To this date, we continue to search for rapidly-acting, available, and safe treatments for depression. Here, we briefly review the latest research from novel compounds with the promise of quick relief of depression.

Ketamine Hydrochloride

The ketamine story for depression roughly began in the year 2000. Several recent high-quality reviews on ketamine's are currently available.[18, 19] Briefly, Berman and colleagues [20] first reported on the rapidly-acting antidepressant properties of a single, slow (40 minutes), subanesthetic (0.5mg/kg) ketamine infusion in 7 unmedicated depressed patients. Within hours, patients had significant improvements in their depression scores following ketamine administration compared to placebo. Several years later, Zarate and

colleagues expanded and replicated these findings at the National Institute of Mental Health's (NIMH) Intramural Research Program in treatment-resistant unipolar [21] and bipolar [22, 23] research patients through randomized, double-blind, placebo-controlled trials. Murrough and colleagues further demonstrated ketamine's significantly superior antidepressant effects by using midazolam as an active comparator, instead of a saline placebo.[24] In addition, ketamine's rapid antisuicidal properties are very promising, as reported in a number of *post-hoc* analyses.[25-27] Though ketamine's antidepressant mechanism of action remains unknown, its effects on the glutamatergic system likely play a role. Ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, represents a departure from the *status quo* of current monoaminergic drug discovery.

Despite ketamine's rapid (within hours) and robust (across a variety of depression symptoms) antidepressant effects when given at low subanesthetic doses, the effects generally do not last longer than seven days (save for patients with certain clinical characteristics, such as anxious depression [28] and a family history of alcoholism,[29] which may predict more robust antidepressant responses). As such, numerous approaches to extend ketamine's action have been reported. For one, several small repeat-dose studies [30-33] have shown promise for extending ketamine's antidepressant effects, though average time-to-relapse is variable and unpredictable among patients. Two studies [34, 35] attempted to prevent depression relapse after a single infusion of ketamine using oral riluzole (an NMDA-receptor antagonist commonly used for the treatment of amyotrophic lateral sclerosis (ALS)) with no significant results. Unfortunately, ketamine's rapid antidepressant effects remain short-lived. Despite this, large strides were made over the past decade and a half in ketamine research, though many questions remain. Several studies are underway to answer these questions, including investigations into ketamine's mechanism of antidepressant action (ClinicalTrials.gov IDs: NCT00088699, NCT02037035) and its ideal antidepressant dose (Ketamine Rapidly-Acting Treatments for Treatment-Resistant Depression (RAPID) study, ClnicalTrials.gov ID: NCT01920555). Esketamine—the S-enantiomer of racemic ketamine—is currently being studied as an adjunct to ongoing antidepressants in patients with treatment-resistant depression (ClnicalTrials.gov ID: NCT02417064) by Janssen, the psychiatric drug division of Johnson & Johnson. If effective and safe, intranasal esketamine could potentially offer patients the ease of at-home administrations (as opposed to the cumbersome in-hospital intravenous ketamine infusions).

Though ketamine has a proven record as a rapidly acting antidepressant in depression research, its side effects are one of the largest barriers to its use as a real world antidepressant. Specifically, the dissociative effects of ketamine—which can include out-of-body experiences and perceptual disturbances—are of particular concern. Although other NMDA receptor antagonists, including memantine[36] and lanicemine,[37] have less side treatment-emergent effects than ketamine, they ultimately failed to show similar robust antidepressant effects of ketamine. Indeed, a crucial mechanism by which ketamine's antidepressant effects are propagated may be through its dissociative properties.[38] In other words, dissociation may be *necessary* for ketamine's antidepressant effects. On the contrary, data from mouse studies suggests that the R-enantiomer of ketamine has rapid antidepressant effects without the dissociative side effects, though human studies are lacking. Regardless of whether or not ketamine's use in the clinic ever comes to fruition, its

potential use as a model for understanding the mechanism by which rapidly acting compounds exert their antidepressant properties remains promising, while evidence for its potential as an antidepressant continues to evolve.

GLYX-13

GLYX-13 (also known as Rapastinel) is a functional partial agonist at the NMDA receptor glycine site. Like ketamine, it is thought to generate its antidepressant mechanism through glutamatergic modulation. In one double-blind, randomized, proof-of-concept study, 116 patients with treatment-resistant depression received a single intravenous infusion of GLYX-13 (doses 1, 5, 10, or 30 mg/kg) or placebo.[39] At doses of 5 and 10mg/kg, GLYX-13 rapidly reduced symptoms of depression within two hours of administration; this effect was maintained for seven days, on average. Unlike ketamine, GLYX-13 did not have significant side effects, including the psychotomimetic effects often associated with ketamine. Though promising, further efficacy and safety studies are currently underway (ClnicalTrials.gov ID: NCT01684163).

Nitrous Oxide

Nitrous oxide, a commonly used inhalational general anesthetic, is a colorless, slightly sweet, non-flammable gas at room temperature. Also called “laughing gas,” nitrous oxide produces euphoria in humans. Because of this, as well as its NMDA receptor antagonist properties,[40] Nagele and colleagues studied the potential antidepressant properties of nitrous oxide.[41] 20 patients with treatment-resistant depression participated in a randomized, placebo-controlled crossover pilot study. Participants received 1-hour of inhaled nitrous oxide (50% nitrous oxide/50% oxygen) or placebo (50% nitrogen/50% oxygen) during the two treatment sessions, each separated by one week. Within two hours, depression symptoms significantly improved with nitrous oxide compared to placebo ($p<0.001$) and remained significant at 24-hours post-administration. Furthermore, 4/20 patients (20%) on nitrous oxide met criteria for response and 3 (15%) met criteria for remission compared to only 1 (5%) patient who met criteria for response on placebo.

Nitrous oxide was generally well tolerated in this study; side effects were brief and of mild-to-moderate severity. Nausea/vomiting was the most reported side effects, occurring in 3 (15%) patients following nitrous oxide and none following placebo. However, long-standing concerns of neurotoxicity arising from preclinical data on nitrous oxide have prompted others to suggest combination techniques—including the use of add-on isoflurane or scopolamine—to prevent the potential neurotoxic side effects of nitrous oxide in the treatment of depression in humans.[42]

Metabotropic Glutamatergic Modulators: Basimglurant and RG1578

Ketamine, nitrous oxide, and GLYX-13 may exert their antidepressant mechanisms through modulation of the *ionotropic* NMDA receptor of the glutamatergic system. In addition, evidence suggests that negative allosteric modulators of the *metabotropic* glutamate receptors (mGluRs) may also play a role in the treatment of depression.[43] Recently,

basimglurant—a potent negative allosteric modulator of the mGluR5—was studied as adjunctive treatment to ineffective antidepressant therapies in adult patients with treatment-resistant depression.[44] In this randomized, double-blind, placebo controlled study of 333 patients, change in total depression scores from baseline in patients on once-daily oral basimglurant did not reach statistical significance at endpoint when measured on the clinician-rated MADRS (week 6; p=0.061); change scores on placebo were similarly insignificant (p=0.127). However, basimglurant was significantly superior to placebo in treating depression when antidepressant improvements were measured on patient-rated scales.

In the same vein, RG1578—a negative allosteric modulator of the mGluR2—was studied as an adjunct to ineffective monoaminergic antidepressant treatments in 310 patients with treatment-resistant depression.[45] However, RG1578 failed to demonstrate any significant antidepressant effects on primary or secondary outcomes. Despite the fact that neither basimglurant or RG1578 were expected to have rapid antidepressant effects, the results suggest that further research is necessary to understand the potential role of metabotropic glutamatergic receptor modulation in the treatment of resistant depression.

Scopolamine

Shifting the focus away from drugs that are thought to exert their primary antidepressant mechanism of action through manipulation of the glutamatergic system, scopolamine has reinvigorated the discussion on the cholinergic system's role in the pathophysiology and treatment of depression, as disruptions to the cholinergic system may play a role in the propagation of mood disorders. [46, 47] This led Furey and Drevets [48] to study the antidepressant potential of scopolamine, an anticholinergic agent that has muscarinic receptor blocking properties. In their first study—a double-blind, placebo-controlled, dose-finding trial—Furey and Drevets initially set out to study the cognitive effects of scopolamine in depression in eight medication-free patients with unipolar or bipolar depression.[48] One dose of placebo and three doses of scopolamine (2.0, 3.0, and 4.0 μg/kg) were administered intravenously over 15-minutes, separated by 3-5 days between infusions. Though not the primary outcome, compared to baseline, mean depression scores (as measured by the Montgomery-Asberg Depression Rating Scale; MADRS) were significantly lower after session 4 (p<0.008). Furthermore, there was a larger decrease in depression scores before vs. after scopolamine dosed at 4.0 μg/kg compared to scores before vs. after placebo (p=0.01).

The serendipitous discovery of scopolamine's antidepressant properties lead Furey and Drevets to conduct a second trial, designed at the outset to study scopolamine's antidepressant efficacy.[48] In this double-blind, placebo-controlled, crossover clinical trial, 19 participants received a single placebo lead-in infusion and then were randomized to receive either 1) placebo (3 sessions) followed by at least one infusion of scopolamine (3 sessions; 4.0 μg/kg), or 2) scopolamine (3 sessions) followed by placebo (3 sessions); infusions were separated by 3-4 days. After the first three sessions, the scopolamine/placebo group had significantly lower depression (MADRS) scores than the placebo/scopolamine

group (p=0.02). Following the final infusion, after which all participants had received scopolamine, depression scores did not differ significantly between the groups (p>0.20).

These initial findings were later replicated in a sample limited to patients with unipolar depression (n=22).[49] Similar to their previous study, Drevets and Furey randomized patients to either a placebo/scopolamine (4.0 μg/kg) or scopolamine/placebo sequence of three infusions for each treatment, for six infusions total. Infusions were 3-5 days apart. Using the MADRS as the primary outcome measure, there was a rapid 32% decrease in depression scores in the scopolamine/placebo group from baseline after the first three infusions (p<0.001). This exceeded the 6.5% decrease in depression scores from baseline in the placebo/scopolamine group after the same timeframe (p=0.009). In the second set of infusions,there was a 53% reduction in depression scores from baseline in the placebo/scopolamine group (p=0.001); the antidepressant effects observed during the first three infusions in the scopolamine/placebo group persisted throughout the placebo portion of the experiment. Patients tolerated scopolamine overall, despite drowsiness, blurred vision, dry mouth, light-headedness, and reduced blood pressure. Though these initial results offer promise, several questions remain regarding scopolamine's ideal dosing, tolerability, and potential real-work efficacy. There is a trial of IV scopolamine augmentation for ECT currently recruiting patients (ClinicalTrials.gov ID: NCT01312844).

Opioid Receptor Modulators

Dysphoria in humans may partly be due to dynorphin activation of kappa-opioid receptors in the brain during chronic stress.[50] Because of this, kappa-opioid receptor antagonists have a theoretical role to play in the treatment of depression. Indeed, preclinical use of the kappa-opioid receptor antagonist hesperidin have been promising in mouse models of depression;[51] furthermore, opioid receptor modulators may have more rapidly-acting mechanisms that traditional monoaminergic antidepressants. As such, several opioid-receptor modulating compounds are of great clinical interest for the treatment of depression. For example, CERC-501—a kappa-opioid receptor antagonist—is currently being studied as an augmentation agent for its potentially rapid-acting antidepressant properties in humans as part of the NIMH-funded RAPID trials (ClinicalTrials.gov ID: NCT01913535). Similarly, ALKS-5461—a combination of buprenorphine (mu-opioid receptor agonist and kappa-opioid receptor antagonist) and samidorphan (a selective mu-opioid receptor antagonist)—is being studied by Alkermes. Compared to placebo, patients randomized to low dose ALKS-5461 (buprenorphine 2mg/samidorphan 2mg) had significant improvements in their depression outcome measures.[52] Despite evidence of improvement in the higher dose ALKS-5461 group (buprenorphine 8mg/samidorphan 8mg), outcome measures did not reach statistical significance. Neither of the ALKS-5461 groups demonstrated evidence of opioid withdrawal symptoms upon stopping the treatment, and overall the treatment was well tolerated. An ongoing study is currently underway to evaluate the antidepressant efficacy of ALKS-5461 in patients with treatment-resistant depression (ClinicalTrials.gov ID: NCT02218008).

Low-Field Magnetic Stimulation (LFMS)

Unlike previously discussed treatments, LFMS approaches the rapid treatment of depression from a non-pharmacologic standpoint. Considered a “neuromodulation” therapy, LFMS is hypothesized to alter brain function via device-based therapy, with the potential to rapidly treat depression. Specifically, LFMS may stimulate the brain by emitting electromagnetic fields (similar to those produced by specific magnetic resonance imaging sequences) via a portable device. One recent study of LFMS augmentation to current antidepressant therapies resulted in rapid improvements (p=0.02) in depression symptoms versus sham treatment after a single, 20-minute session in a combined sample of patients with unipolar (n=22) and bipolar (n=41) depression; the authors caution that the primary analyses (which stratified by diagnosis) did not yield significance.[53] Nonetheless, LFMS is classified by the FDA under a nonsignificant risk determination, and holds promise as a relatively well-tolerated augmentation agent for depression. Investigations are currently underway, including an LFMS study as part of the NIMH's RAPID trials (ClinicalTrials.gov ID: NCT01654796).

Conclusions

The treatment of depression is undergoing a paradigm shift. Namely, drugs that act rapidly —within hours to days, instead of weeks to month—are now at the forefront of research. Several of these drugs—namely, ketamine, nitrous oxide, and scopolamine—have all been repurposed from their originally intended uses as anesthetics (ketamine and nitrous oxide) and antinausea/antisecretion (scopolamine) medications. Interestingly, compared to our current classes of approved antidepressant agents, these drugs commonly alter perceptional experiences. Is there something necessary and/or sufficient within those processes that lead to rapidly acting antidepressant properties? For example, unlike psychotomimetic and sympathomimetic side effects, evidence exists to suggest that ketamine's dissociative properties mediate its antidepressant properties.[38]

Although we attempt to classify drugs based on their primary mechanism of action, these “monoaminergic,” “glutamatergic,” and “anticholinergic,” these medications likely cause complex changes in the brain that extend beyond such straightforward categories. For one example, Williams and Schatzberg [54] suggested that an “entourage effect” may be responsible for ketamine's antidepressant properties, rather than the sole reliance on NMDA receptor antagonism as the explanation. In this view, ketamine's actions extend beyond that of glutamatergic receptor antagonism, to include actions on the dopaminergic and opioid systems. Combined, these mechanisms act synergistically, thereby resulting in a rapid antidepressant phenomenon. Ultimately, this complex interplay of neurotransmitter modulations may lead to neuronal remodeling, including increased neuronal plasticity and enhanced neurocircuits—thereby changing the dysfunctional structure of the depressed brain, as opposed to merely affixing a neurotransmitter-balancing “band aid.”

Regardless of whether or not rapidly-acting antidepressants come into standard clinical use, they may provide our field with the models needed to delve deeper into understanding the pathophysiology of depression. This, in turn, can ultimately lead to uncovering the mechanisms behind rapidly-acting antidepressants, ultimately leading to targeted drug

discovery. Only time will tell as to whether our understanding of depression fits more of an Occam's razor explanation, or if the brain—especially the depressed brain—is truly one of the most complex structures in the universe. Nonetheless, it is our prerogative to keep patients in mind throughout this process of discovery, as millions of people worldwide continue to suffer and die from this serious and unrelenting illness every year.

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