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CME Review Article

New Medications for Treatment-Resistant Depression: A Brief Review of Recent Developments

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New medications for treatment-resistant depression: a brief review of recent developments

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There is a great unmet need for new medications with novel mechanisms of action that can effectively treat patients who do not benefit from standard antidepressant therapies. After a period in which it seemed as if the pharmaceutical pipeline for new antidepressants was going dry, the past decade has witnessed renewed interest, beginning with discovery of the antidepressant effects of ketamine. This article briefly highlights more recent research on ketamine and other investigational antidepressants.

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Introduction

The 1980s and 1990s were a time of what seemed like unlimited efforts by the pharmaceutical industry to develop novel treatments for depression, which led to the introduction of more than a dozen new medications. However, the investigational pipeline had largely dried up by the end of the first decade of the 21st century. As a result, current practice is dominated by use of generic formulations of the more commonly prescribed selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and several other antidepressants (i.e., bupropion and mirtazapine) that target other aspects of monoaminergic neurotransmission.^{1,2} These generally safe and well-tolerated medications are tangibly easier to prescribe than their predecessors, and much first-line treatment of depression is now capably handled by primary care providers. Nevertheless, as underscored by the results of the massive STAR*D study, in which about one-third of the patients who began treatment remained depressed despite up to 4 sequential treatment trials,³ there remains a great unmet need for patients who do not respond to conventional therapies. Moreover, this challenge has been only partly met by more recent developments for patients with treatment-resistant

depression (TRD), as a majority of patients who do not respond to first-line agents also do not respond to various combinations of newer generation antidepressants and adjunctive therapy with second generation antipsychotics.^{4,5} As disproportionate shares of the heavy interpersonal, medical, and societal burdens associated with depression are attributable to those patients suffering from more advanced cases of TRD, development of new treatments that work through novel mechanisms of action will be a particularly welcomed advance in psychiatric therapeutics. This article will briefly review several investigational strategies that may indeed provide new hope for patients with TRD.

Ketamine

Like the initial discoveries of the antidepressant effects of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), what may be soon called the “ketamine era” of psychiatric therapeutics began with a serendipitous observation.⁶ Specifically, ketamine—a dissociative anesthetic with some abuse liability (it is classified as a Schedule III drug by the Drug Enforcement Administration [DEA]) that has been in use since the late 1960s—was given in sub-anesthetic intravenous doses in a study of individuals at increased risk of psychosis and, unexpectedly, some of these subjects reported significant relief of depressive symptoms. These very preliminary observations were first corroborated in a 9 subject study using a crossover design,⁷ and subsequently extended by a pair of small, but well-controlled, studies using parallel

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group design conducted at the National Institute of Mental Health.^{8,9} Today, after an additional decade of research, the rapid and robust antidepressant effects of ketamine have been extensively replicated.^{10,11} It is now clear that 0.4–0.6 mg/kg of ketamine, typically infused over approximately 30–60 minutes, can exert a dramatic antidepressant effect in 40%–60% of depressed patients.

Unlike all of the conventional medical therapies for depression, the antidepressant effects of a ketamine infusion are often evident within the first 24 hours and typically persist for up to 7 days, ie, long after the potentially intoxicating effects of the drug have passed.^{10,11} The rapidity of ketamine's antidepressant effects thus offers special promise for use in psychiatric inpatient settings, where each day of care costs more than \$1000. The effects of ketamine infusions on the suicidal ideations appear to be as rapid—and of comparable magnitude—as its effects on mood and core depressive symptoms.¹² Thus, emergency room dosing of ketamine might also prove to be helpful to shorten or even avoid hospitalizations when patients present in acute suicidal crises. Conversely, clinical experience suggests that a large majority of individuals who will respond to ketamine do so within the first 1–4 infusions. Thus, the decision to stop a course of ketamine infusion therapy for futility can be made relatively quickly, which minimizes the costs associated with an ineffective course of treatment.

Despite the rapidity of the effects of ketamine, the imperistence of the therapeutic benefit, which usually dissipates over 4–6 days, underscores the clinical observation that most patients who respond to ketamine need an ongoing course of continuation phase therapy (ie, once- or twice-weekly infusions over at least several months).¹³ There are no data yet from well-controlled studies of longer courses of therapy, and it is possible that some or even most ketamine responders require an indefinite course of maintenance phase infusions.¹⁴ It also is not known if the efficacy of ketamine infusion therapy can be sustained with less costly alternative means of parenteral administration, such as intramuscular, intranasal, or sublingual delivery.

There are a number of reasons to be cautious about the increasing use of ketamine.^{14–16} Importantly, at present use of ketamine in any form to treat depression represents an off-label use of a controlled substance with a long-recognized abuse liability. For this reason, it should be considered an experimental or investigational treatment and only considered when conventional therapies have failed.¹⁵ With respect to central nervous system side effects, up to 50% of depressed patients experience transient euphoric, dissociative, or psychotomimetic effects at the doses used to treat depression.¹⁰ The “trippy” side effects of ketamine typically dissipate within 60 minutes, and, interestingly, there is no clear correlation between the intensity of these effects and the likelihood or magnitude of therapeutic effects.¹⁴

Other common transient side effects include cognitive impairment, sedation, and high blood pressure.¹⁰ For these reasons, it is important to monitor vital signs throughout a course of intravenous treatment, and infusion therapy requires a level of medical oversight that is well beyond that available in most outpatient psychiatric settings. Indeed, in some settings, ketamine infusions are overseen by a nurse anesthetist or anesthesiologist.

Foremost among concerns about longer term use is the need to establish both the safety and efficacy of repeated infusions of ketamine beyond a few weeks. With respect to efficacy, there is a clear imperative to document whether some patients will develop a progressive tolerance to the antidepressant effects over months of ketamine therapy. These concerns are particularly warranted because individuals who abuse ketamine for its psychoactive effects often develop tolerance fairly rapidly with repeated doses and typically substantially escalate the dose taken over the course of a period of sustained use. The risks associated with such misuse of ketamine include both persistent cognitive impairments and neuroradiologic evidence of neurotoxicity, as well as an aseptic cystitis.¹⁰ Thus, until the safety of longer term therapy with lower doses of ketamine is established, it is imperative to ensure the safety of our patients who appear to require maintenance therapy.¹⁷ Some reassurance can be derived from the anecdotal clinical experiences of ketamine clinics that are proliferating around the US and several other countries, although the value of these data are limited by the nonsystematic nature of safety assessments and follow-ups.¹⁷ It is hoped that the recently proposed guidelines developed under the auspices of the American Psychiatric Association for the clinical use of ketamine for treatment of depression can result in both a greater consistency in the quality of care delivered and ensure collection of safety data.¹⁷

Related Therapies Targeting NMDA Receptors

One potentially far-reaching consequence of recognition of the antidepressant effects of ketamine is that it has fostered renewed interest in psychiatric drug discovery. The lack of association between the “psychedelic” and antidepressant effects of ketamine strongly suggests that it may be possible to differentiate the mechanism(s) of beneficial effect from those actions that are associated with abuse liability.¹⁴ With respect to mechanisms of action, the therapeutic effects of ketamine are presumed to begin, at least in part, with competitive (or, perhaps more correctly, non-competitive) antagonism of N-methyl-D-aspartate (NMDA) receptors on glutamate neurons.⁶ Neurons that express NMDA receptors are among the most ubiquitous in the brain, and an

increasing body of research has implicated this excitatory amino acid in the pathophysiology of depression, including the processes that impress the resilience of neuronal systems to stress.⁶ Ketamine and its metabolites also modulate α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and μ opiate receptors, and, in animal studies, these effects in aggregate can rapidly restore stress-induced decreases in neuronal connectivity.⁶ In human studies, ketamine infusions also produce large changes in the connectivity of neural circuits associated with cognitive-affective processes associated with depression.¹⁸ To what extent these changes can become enduring with extended treatment remains to be seen. Likewise, the possibility that a brief series of ketamine infusions might restore the brain's capacity to respond to conventional antidepressant medications has not (yet) been tested.

Esketamine

Obviously, the lowest hanging fruit in the orchard of drug development came from the fact that ketamine is a racemic molecule and both the R- and S-enantiomers possess antidepressant activity in preclinical models.⁶ The S-enantiomer, now known as esketamine, is also a US Food and Drug Administration (FDA)-approved anesthetic, and both clinical experience¹⁹ and a small pilot study of intravenous infusion²⁰ have suggested antidepressant effects comparable to racemic ketamine. Given the costs and associated logistical issues resulting from intravenous delivery, one pharmaceutical company is commercially developing esketamine with a novel intranasal delivery device (see, for example, the phase 1 safety study of van de Loo *et al.*²¹). Although there are no data from controlled studies of intranasal delivery of esketamine yet in the published literature, a phase 3 research program in TRD (NCT01780259) is nearing completion, and a second program evaluating esketamine for treatment of major depressive disorder in patients at imminent suicide risk (NCT03039192) is underway. Both of these research programs have been given the Breakthrough Drug designation by the FDA.

Rapastinel

Among the compounds not directly tied to ketamine, rapastinel (formerly known as GLYX-13) is arguably next in line with respect to the likelihood of reaching the market as an approved treatment for major depressive disorder (MDD). Also designated by the FDA as a Breakthrough Drug, this compound was synthesized on the basis of a receptor modeling strategy and is thought to be a partial agonist of an allosteric glycine site of the NMDA receptor.²² The potential promise of this drug as an antidepressant is underpinned by a large number of

preclinical studies (see Moskal *et al.*²²). In the only randomized clinical trial published to date,²³ 116 depressed patients with a history of nonresponse to at least one conventional antidepressant in the current episode were randomly assigned to either an inert placebo or a single intravenous infusion of one of 4 doses of rapastinel (1, 5, 10, or 30 mg/kg). Results suggested that, like ketamine, response to intravenous therapy with rapastinel appeared to show a curvilinear relationship, with significant benefit within 2 hours of infusion at doses of 5 or 10 mg/kg; patients who received doses of 1 or 30 mg/kg did not show a significant antidepressant effect compared to the double-blind placebo. Unlike ketamine, the antidepressant effects of rapastinel appeared to persist for 1 week, and no dose showed any sedative, dissociative, or psychotomimetic side effects. A phase three program evaluating adjunctive therapy for TRD began in early 2017 (see NCT02943564), and a study evaluating the sustained efficacy of adjunctive rapastinel for relapse prevention of MDD also recently began (NCT02951988); additional studies focusing on rapid relief of suicidal ideation are being planned.

Other NMDA receptor antagonists

Not all drugs that engage NMDA receptors have been shown to have significant antidepressant effects. Perhaps the most sobering example is the development program for lanicemine—a drug described as a low trapping NMDA channel blocker²⁴—which came to a crashing halt despite a promising preclinical and early clinical development program. The commercial demise of lanicemine resulted from 1 failed phase 3 trial.²⁵ This 12-week study evaluated 2 doses of intravenous lanicemine (50 and 100 mg) as an adjunctive therapy in 302 depressed patients with a history of nonresponse to antidepressants. Although lanicemine was well-tolerated, neither dose showed a significant antidepressant effect in comparison to double blind placebo.²⁵ Although failed trials are commonly observed in the phase 3 programs of commercially successful antidepressants, the manufacturer judged that, on the basis of these findings, the probability that lanicemine would subsequently be shown to have ketamine-like antidepressant effects was not high enough to justify further investment in large scale clinical studies.

Other compounds that have relative weak modulatory effects on NMDA receptors, including drugs that have been approved by the FDA for other indications, including lamotrigine (epilepsy and bipolar disorder), memantine (Alzheimer's disease), and riluzole (amyotrophic lateral sclerosis), have failed to either show strong antidepressant effects in TRD or sustain the therapeutic effects of ketamine.⁶

Drugs Targeting the Opiate System

Another investigational strategy for adjunctive treatment of depression addresses the intriguing relationships between the endogenous opiate system and dysphoria, despair, pleasure, and the anticipation of reward.^{26–28} This is a historically rich topic: it has long been known that some severely depressed individuals experience a significant lift in mood when administered potent opiates and, in Victorian times, various patent medicines containing opium were prescribed to lessen the misery of people suffering from melancholia. However, the risks of regular use of opiates also have been recognized for many decades, and these concerns have been amplified by the recent epidemic of opiate abuse and the significant increase in deaths associated with opiate overdoses.

The medical and sociocultural factors that have functionally blocked research on putative antidepressant drugs that modulate the endogenous opiate system may be addressed by the concomitant use of selective agonists and antagonists for specific types of opiate receptors.²⁹ Buprenorphine, a μ - and κ -opioid partial agonist that is approved by the FDA for the treatment of pain and opiate addiction, has shown some antidepressant effects in case series and small-scale open studies.^{30,31} However, this Schedule V controlled substance has too much abuse liability itself for regular use in less complicated forms of MDD. More recently, samidorphan, an investigational μ -opioid antagonist, has been added to buprenorphine as a means to minimize the undesirable opiate effects and negate abuse liability.²⁹ Now known as ALKS-5461, the combination medication is administered as a sublingual formulation containing equal amounts of the two components.²⁹ The initial proof of concept study of this combination, which was conducted in patients with TRD receiving ongoing antidepressant therapy, utilized 2 sequential 4-week, placebo controlled stages. In this trial, there was a significant antidepressant effect for the patients in the arm that receive 2 mg/2 mg; results in the arm that received higher doses were more equivocal.³² Importantly, there were no signs of opiate withdrawal at the end of each phase of the double blind protocol. A Phase 3 development program focusing on adjunctive therapy of patients with TRD is nearing completion, although it has been reported that several of the studies did not observe statistically significant results (see: <http://www.fiercebiotech.com/biotech/will-third-trial-be-charm-for-alkermes-depression-drug>) and an additional study is underway (see NCT03188185).

Other Drugs with Abuse Liability

Serious consideration of the potential clinical benefits of several drugs with definite abuse liability has led to a re-examination of other drugs for patients with TRD that just a few years ago would not even have been considered.

This list includes small studies of another anesthetic, nitrous oxide (aka “laughing gas”),³³ and the hallucinogenic compound psilocybin (“magic mushrooms”).^{34,35} Only time and continued careful study in tightly controlled experiments will help to determine whether these uncommon and less traveled therapeutic roads will lead to confirmation of meaningful benefit for patients who do not respond to standard therapies.

Is Immune Dysfunction the Next Target for Drug Development?

Another potential target for adjunctive therapy was derived from the rapidly growing work linking persistent or unremitting depression to chronic inflammation and high levels of inflammatory cytokines and other “markers” (including Interleukin-1 and Interleukin-6 [IL-1; IL-6], Tumor Necrosis Factor alpha [TNF α], C Reactive Protein [CRP], and monocyte chemoattractant protein-1 [MCP-1]).^{36,37} It appears that high levels of nonspecific inflammatory markers such as CRP may be associated with poorer response to SSRI monotherapy,^{38–40} but possibly not to the TCA nortriptyline³⁹ or adjunctive bupropion.⁴⁰ Similarly, preliminary studies of adjunctive use of anti-inflammatory medications, such as selective cyclooxygenase 2 inhibitor celecoxib and tumor necrosis factor antagonist infliximab,³⁸ show promise, particularly for patients showing elevated peripheral markers of inflammation.^{40,41} Whether these interesting findings will be replicable on a larger scale remains to be seen, though it is hoped that this line of research will lead to a newer generation of adjunctive treatment strategies for a selected subgroup of depressed patients with difficult-to-treat depression.

Conclusions

In one short decade, research on novel antidepressants has shifted remarkably from drugs that target monoamine systems to drugs that modulate glutamatergic, opiate, and other neurotransmitter systems. As exemplified by the discovery of ketamine's antidepressant effects, the combination of serendipity and keen clinical observation continues to play a role in drug discovery. The excitement that invariably accompanies such discoveries must, of course, be tempered by the need to systematically evaluate the potential benefits and limitations of these putative treatments. As several new drugs with novel mechanisms of action advance through the FDA approval process, it seems likely that additional effective therapies may soon be available for patients with more advanced stages of TRD.

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Optional Posttest and CME Certificate

CME Credit Expires: November 30, 2020

Posttest Study Guide

NOTE: The posttest can only be submitted online. The below posttest questions have been provided solely as a study tool to prepare for your online submission. **Faxed/mailed copies of the posttest cannot be processed** and will be returned to the sender. If you do not have access to a computer, contact NEI customer service at 888-535-5600.

1. Studies have shown that 0.4-0.6mg/kg of ketamine, typically infused over approximately _____ minutes, can exert a dramatic antidepressant effect in 40%-60% of depressed patients.
 - A. 5 - 20
 - B. 30 - 60
 - C. 60 - 120
 - D. 120 - 180
2. Which of the follow novel compounds is thought to be a partial agonist of an allosteric glycine site of the NMDA receptor:
 - A. Ketamine
 - B. Esketamine
 - C. Rapastinel
 - D. Riluzole
 - E. Lanicemine
3. A novel compound being investigated, ALKS-5461, is administered as a sublingual formulation containing equal amounts of two components: Buprenorphine, a μ - and κ -opioid partial agonist, and samidorphan, an investigational _____.
 - A. κ -opioid partial agonist
 - B. δ -opioid antagonist
 - C. μ -opioid agonist
 - D. μ -opioid antagonist
 - E. κ -opioid partial antagonist

Optional Online Posttest and CME Certificate Instructions

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1. Read the article.
2. Complete the posttest and evaluation, available only online at www.neiglobal.com/CME (under “CNS Spectrums”).
3. Print your certificate (passing score = 70% or higher).

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