CNS SPECTRUMS

CME Review Article

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

This activity is provided by the Neuroscience Education Institute.

Additionally provided by the American Society for the Advancement of Pharmacotherapy.

American Society for the Advancement of Pharmacotherapy
Division 55, American Psychological Association

https://doi.org/10.1017/S1092852917000876 Published online by Cambridge University Press

CME Information

Date of Release/Expiration

Released: December, 2017
CME credit expires: November, 2020

Learning Objective

After completing this activity, you should be better able to describe the molecular targets of novel agents, including adjunctive treatments, currently being investigated for applicability in the treatment of major depressive disorder

Accreditation and Credit Designation Statements

The Neuroscience Education Institute (NEI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

NEI designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Society for the Advancement of Pharmacotherapy (ASAP), Division 55 of the American Psychological Association, is approved by the American Psychological Association to sponsor continuing education for psychologists. ASAP maintains responsibility for this program and its content.

The American Society for the Advancement of Pharmacotherapy designates this program for 1.0 CE credit for psychologists.

Nurses and *Physician Assistants:* for all of your CE requirements for recertification, the ANCC and NCCPA will accept *AMA PRA Category 1 Credits*™ from organizations accredited by the ACCME. The content of this activity pertains to pharmacology and is worth 1.0 continuing education hour of pharmacotherapeutics.

Instructions for Optional Posttest and CME Credit

The estimated time for completion of this activity is 60 minutes. There is no posttest fee nor fee for CME credits.

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)

Questions? call 888-535-5600, or email CustomerService@neiglobal.com

Peer Review

This content has been peer reviewed by an MD specializing in psychiatry to ensure the scientific accuracy and medical relevance of information presented and its independence from commercial bias. NEI takes responsibility for the content, quality, and scientific integrity of this CME activity.

Disclosures

All individuals in a position to influence or control content are required to disclose any financial relationships. Although potential conflicts of interest are identified and resolved prior to the activity being presented, it remains for the participant to determine whether outside interests reflect a possible bias in either the exposition or the conclusions presented.

Disclosed financial relationships with conflicts of interest have been reviewed by the NEI CME Advisory Board Chair and resolved.

Author

Michael E. Thase, MD, is a professor in the Department of Psychiatry and Director of the Mood and Anxiety Disorders Treatment and Research Program of the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, PA. Dr. Thase receives research support from the Agency for Healthcare Research and Quality, Alkermes, AssureRx, Avanir, Forest, Intracellular, Janssen, Lilly, National Institutes of Health, Otsuka, and Takeda, and is a consultant/advisor to Alkermes, Allergan, AstraZeneca, Bristol-Myers Squibb, Cerecor, Fabre-Kramer, Forest, Gerson Lehman, GlaxoSmithKline, Guidepoint Global, H. Lundbeck, Lilly, MedAvante, Merck, Moksha8, Neuronetics, Ortho-McNeil, Otsuka, Pamlab (Nestle), Pfizer, Roche, Shire, Sunovion, Takeda, and Trius. Dr. Thase has equity holdings in MedAvante and receives royalties from the American Psychiatric Foundation, Guilford Publications, Herald House, MedAvante, and W.W. Norton & Company. Dr. Thase's spouse is employed by Peloton Advantage.

No writing assistance was utilized in the production of this article.

CNS Spectrums Peer Review

All CME articles are peer reviewed in accordance with the strict standards of *CNS Spectrums* and in accordance with requirements and recommendations of the International Committee of Medical Journal Editors. The Editorial policies of the journal *CNS Spectrums* and peer

https://doi.org/10.1017/S1092852917000876 Published online by Cambridge University Press

review of all articles that appear in the journal is managed independently by Cambridge University Press and no financial relationship exists between the CME provider and Cambridge for this service.

Additional Peer Reviewer

Ronnie Gorman Swift, MD, is a professor in and associate chairman of the department of psychiatry and behavioral sciences at New York Medical College in Valhalla, NY, and the chief of psychiatry and associate medical director at Metropolitan Hospital Center in New York, NY. Dr. Swift has no financial relationships to disclose.

The **Content Editor** and **Planning Committee** have no financial relationships to disclose.

Disclosure of Off-Label Use

This educational activity may include discussion of unlabeled and/or investigational uses of agents that are not currently labeled for such use by the FDA. Please consult the product prescribing information for full disclosure of labeled uses.

Cultural and Linguistic Competency

A variety of resources addressing cultural and linguistic competency can be found at this link: www.neiglobal.com/go/cmeregs

Provider

This activity is provided by NEI. Additionally provided by ASAP.

Acknowledgment of Financial Support

This activity is supported by an unrestricted educational grant from Alkermes.

CNS Spectrums (2017), **22**, 42–47.
doi:10.1017/S1092852917000876

REVIEW ARTICLE

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

*Michael E. Thase**

Department of Psychiatry, Perelman School of Medicine of the University of Pennsylvania, Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA

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.

Received 30 October 2017; Accepted 4 December 2017

Key words: ALKS-5461, esketamine, investigational antidepressants, ketamine, rapastinel, treatment-resistant depression, therapies.

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

* Address for correspondence: Michael E. Thase, MD, Perelman School of Medicine, 3535 Market Street, Suite 670, Philadelphia, PA 19104, USA. (Email: thase@pennmedicine.upenn.edu)

This activity is supported by an unrestricted educational grant from Alkermes.

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 impersistence 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-noncompetitive) 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

https://doi.org/10.1017/S1092852917000876 Published online by Cambridge University Press

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 experience[19] and a small pilot study of intravenous infusion[20] 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 blocker[24]—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]

https://doi.org/10.1017/S1092852917000876 Published online by Cambridge University Press

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 continuing 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 [TNFα], 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 nortriptyline[39] 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.

Disclosures

Michael Thase has the following disclosures: Alkermes, grant and personal fees, grant recipient and consultant;

https://doi.org/10.1017/S1092852917000876 Published online by Cambridge University Press

AstraZeneca, personal fees, consultant; Bristol-Myers Squibb Company, personal fees, consultant; Eli Lilly & Co., grant and personal fees, grant recipient and consultant; Forest Laboratories, grant and personal fees, grant recipient and consultant; Gerson Lehman Group, personal fees, consultant; GlaxoSmithKline, personal fees, consultant; Guidepoint Global, personal fees, consultant; H. Lundbeck A/S, personal fees, consultant; MedAvante, personal fees, consultant, equity holdings; Merck and Co., personal fees, consultant; Neuronetics, Inc., personal fees, consultant; Ortho-McNeil Pharmaceuticals, personal fees, consultant; Otsuka, grant and personal fees, grant recipient and consultant; Pfizer, personal fees, consultant; Roche, personal fees, consultant; Shire US, Inc., personal fees, consultant; Sunovion Pharmaceuticals, Inc., personal fees, consultant; Takeda, personal fees, consultant; American Psychiatric Foundation, royalties; Guilford Publications, royalties; Herald House, royalties; W.W. Norton & Company, Inc., royalties; Peloton Advantage, spouse's employment; Cerecor, Inc., personal fees, consultant; Moksha8, personal fees, consultant; Pamlab, L.L.C. (Nestle); Allergan, personal fees, consultant; Trius Therapeutical, Inc., personal fees, consultant; Fabre-Kramer Pharmaceuticals, Inc., personal fees, consultant; Agency for Healthcare Research and Quality, grant, grant recipient; AssureRx, grant, grant recipient; Avanir, grant, grant recipient; Forest Pharmaceuticals, grant, grant recipient; Janssen, grant, grant recipient; Intracellular, grant, grant recipient; National Institutes of Health, grant, grant recipient; Takeda, grant, grant recipient.

REFERENCES:

1. Gelenberg AJ, Freeman MP, Markowitz JC, *et al*. Practice guidelines for the treatment of patients with major depressive disorder (third edition). *Am J Psychiatry*. 2010; **167**(10): 9–118.
2. Kennedy SH, Lam RW, McIntyre RS, *et al*; CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. *Can J Psychiatry*. 2016; **61**(9): 540–560.
3. Rush AJ, Trivedi MH, Wisniewski SR, *et al*. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006; **163**(11): 1905–1917.
4. Thase ME. Antidepressant combinations: widely used, but far from empirically validated. *Can J Psychiatry*. 2011; **56**(6): 317–323.
5. Thase ME. Adverse effects of second-generation antipsychotics as adjuncts to antidepressants: are the risks worth the benefits? *Psychiatr Clin North Am*. 2016; **39**(3): 477–486.
6. Abdallah CG, Averill LA, Krystal JH. Ketamine as a promising prototype for a new generation of rapid-acting antidepressants. *Ann N Y Acad Sci*. 2015; **1344**: 66–77.
7. Berman RM, Cappiello A, Anand A, *et al*. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000; **47**(4): 351–354.
8. Zarate CA Jr, Singh JB, Carlson PJ, *et al*. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006; **63**(8): 856–864.
9. Diazgranados N, Ibrahim L, Brutsche NE, *et al*. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. 2010; **67**(8): 793–802.
10. Newport DJ, Carpenter LL, McDonald WM, Potash JB, Tohen M, Nemeroff CB, APA Council of Research Task Force on Novel Biomarkers and Treatments. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry*. 2015; **172**(10): 950–966.
11. Han Y, Chen J, Zou D, *et al*. Efficacy of ketamine in the rapid treatment of major depressive disorder: a meta-analysis of randomized, double-blind, placebo-controlled studies. *Neuropsychiatr Dis Treat*. 2016; **12**: 2859–2867.
12. Wilkinson ST, Ballard ED, Bloch MH, *et al*. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry*. In press. doi: 10.1176/appi.ajp.2017.17040472.
13. Lener MS, Kadriu B, Zarate CA Jr. Ketamine and beyond: investigations into the potential of glutamatergic agents to treat depression. *Drugs*. 2017; **77**(4): 381–401.
14. Malhi GS, Byrow Y, Cassidy F, *et al*. Ketamine: stimulating antidepressant treatment? *BJPsych Open*. 2016; **2**(3): e5–e9.
15. Sisti D, Segal AG, Thase ME. Proceed with caution: off-label ketamine treatment for major depressive disorder. *Curr Psychiatry Rep*. 2014; **16**(12): 527.
16. Sanacora G, Schatzberg AF. Ketamine: promising path or false prophecy in the development of novel therapeutics for mood disorders? *Neuropsychopharmacology*. 2015; **40**(2): 259–267.
17. Sanacora G, Frye MA, McDonald W, *et al*; American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*. 2017; **74**(4): 399–405.
18. Abdallah CG, Averill CL, Salas R, *et al*. Prefrontal connectivity and glutamate transmission: relevance to depression pathophysiology and ketamine treatment. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2017; **2**(7): 566–574.
19. Correia-Melo FS, Argolo FC, Araújo-de-Freitas L, *et al*. Rapid infusion of esketamine for unipolar and bipolar depression: a retrospective chart review. *Neuropsychiatr Dis Treat*. 2017; **13**: 1627–1632.
20. Singh JB, Fedgchin M, Daly E, *et al*. Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. *Biol Psychiatry*. 2016; **80**(6): 424–431.
21. van de Loo AJAE, Bervoets AC, Mooren L, *et al*. The effects of intranasal esketamine (84 mg) and oral mirtazapine (30 mg) on on-road driving performance: a double-blind, placebo-controlled study. *Psychopharmacology (Berl)*. 2017; **234**(21): 3175–3183.
22. Moskal JR, Burgdorf JS, Stanton PK, *et al*. The development of rapastinel (formerly GLYX-13); a rapid acting and long lasting antidepressant. *Curr Neuropharmacol*. 2017; **15**(1): 47–56.
23. Preskorn S, Macaluso M, Mehra DO, Zammit G, Moskal JR, Burch RM, GLYX-13 Clinical Study Group. Randomized proof of concept trial of GLYX-13, an N-methyl-D-aspartate receptor glycine site partial agonist, in major depressive disorder nonresponsive to a previous antidepressant agent. *J Psychiatr Pract*. 2015; **21**(2): 140–149.
24. Sanacora G, Smith MA, Pathak S, *et al*. Lanicemine: a low-trapping NMDA channel blocker produces sustained antidepressant efficacy with minimal psychotomimetic adverse effects. *Mol Psychiatry*. 2014; **19**(9): 978–985.
25. Sanacora G, Johnson MR, Khan A, *et al*. Adjunctive lanicemine (AZD6765) in patients with major depressive disorder and history of

inadequate response to antidepressants: a randomized, placebo-controlled study. *Neuropsychopharmacology*. 2017; **42**(4): 844–853.
26. Panksepp J, Yovell Y. Preclinical modeling of primal emotional affects (seeking, panic and play): gateways to the development of new treatments for depression. *Psychopathology*. 2014; **47**(6): 383–393.
27. Rantala MJ, Luoto S, Krams I, Karlsson H. Depression subtyping based on evolutionary psychiatry: proximate mechanisms and ultimate functions. *Brain Behav Immun*. 2017. In press. doi: 10.1016/j.bbi.2017.10.012.
28. Peciña M, Bohnert AS, Sikora M, *et al*. Association between placebo-activated neural systems and antidepressant responses: neurochemistry of placebo effects in major depression. *JAMA Psychiatry*. 2015; **72**(11): 1087–1094.
29. Ehrich E, Turncliff R, Du Y, *et al*. Evaluation of opioid modulation in major depressive disorder. *Neuropsychopharmacology*. 2015; **40**(6): 1448–1455.
30. Karp JF, Butters MA, Begley AE, *et al*. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. *J Clin Psychiatry*. 2014; **75** (8): e785–e793.
31. Stanciu CN, Glass OM, Penders TM. Use of buprenorphine in treatment of refractory depression—a review of current literature. *Asian J Psychiatr*. 2017; **26**: 94–98.
32. Fava M, Memisoglu A, Thase ME, *et al*. Opioid modulation with buprenorphine/samidorphan as adjunctive treatment for inadequate response to antidepressants: a randomized double-blind placebo-controlled trial. *Am J Psychiatry*. 2016; **173**(5): 499–508.
33. Nagele P, Duma A, Kopec M, *et al*. Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial. *Biol Psychiatry*. 2015; **78**(1): 10–18.
34. Griffiths RR, Johnson MW, Carducci MA, *et al*. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. *J Psychopharmacol*. 2016; **30**(12): 1181–1197.
35. Ross S, Bossis A, Guss J, *et al*. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol*. 2016; **30**(12): 1165–1180.
36. Köhler CA, Freitas TH, Maes M, *et al*. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand*. 2017; **135**(5): 373–387.
37. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016; **16**(1): 22–34.
38. Köhler O, Benros ME, Nordentoft M, *et al*. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry*. 2014; **71**(12): 1381–1391.
39. Uher R, Tansey KE, Dew T, *et al*. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. *Am J Psychiatry*. 2014; **171**(12): 1278–1286.
40. Jha MK, Minhajuddin A, Gadad BS, *et al*. Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. *Psychoneuroendocrinology*. 2017; **78**: 105–113.
41. Raison CL, Rutherford RE, Woolwine BJ, *et al*. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry*. 2013; **70**(1): 31–36.

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

There is no posttest fee nor fee for CME credits.

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).

Questions? call 888-535-5600, or email CustomerService@neiglobal.com

https://doi.org/10.1017/S1092852917000876 Published online by Cambridge University Press