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This activity is intended for physicians, physician assistants, nurse practitioners and registered nurses engaged in the care of patients with major depression.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Treat major depression within 2 weeks.
- Use evidence based treatments to achieve remission in major depression.
- Discuss novel targets including glutamate for treating major depression.
- Utilize treatments with innovative mechanisms to treat major depression.

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SUPPLEMENT TO
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Targeting Unmet Needs in the Treatment of Major Depressive Disorder

Roger S. McIntyre, MD, FRCPC

BOTTOM LINE: Targeting Unmet Needs in the Treatment of Major Depressive Disorder

Many of the unmet needs in Major Depressive Disorder are modifiable, including improving diagnostic accuracy, offering treatments with faster onset of action, treatments with greater overall efficacy, and treatments that can improve patient functioning. Measurement based care guiding treatment wherein the aim is to achieve remission, improve cognitive function, and general functioning, are key therapeutic objectives.

Introduction

Major depressive disorder (MDD) is a common and severe disorder that is estimated to affect approximately 350 million people globally.[1] It is predicted that MDD debases human capital more than most other non-communicable disorders.[2] In addition to substantial illness-associated morbidity, MDD is associated with the loss of 10 years of life.[3] The implications of MDD on other organ systems is demonstrated by mortality studies indicating that cardiovascular disease is the most common cause of excess mortality.[4] Significant unmet needs exist in the management of MDD, which, if addressed successfully, would be expected to reduce overall illness-associated morbidity. Herein, we succinctly review and summarize key unmet needs in MDD (***Table 1***).

Identifying which patients will respond to which treatments

The inability to identify a priori which individuals will (and will not) respond to and tolerate a chosen antidepressant often leads to multiple trials of futility, adverse therapeutic outcomes, and unnecessary prolongation of MDD disease activity. The promise of pharmacogenetics/pharmacogenomics brings the possibility of closing the gap between the current practice of iteratively selecting antidepressants toward a bespoke selection of antidepressants in MDD.[5] Pharmacogenetics testing refers to evaluating a single allelic variation, while pharmacogenomic testing integrates allelic variance for proteins that participate in both pharmacokinetic and/or pharmacodynamic processes.[5] The rationale for considering a given patient's

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TABLE 1

Unmet needs in major depressive disorder

1) Need to identify which patients with MDD will respond to/tolerate (or not) antidepressant therapies (ie, personalized medicine).
2) Treatments that are more (or less) likely to achieve provider- and patient-desired outcomes (PROs) in MDD.
3) Treatments capable of attenuating critical dimension/domain-based outcomes in MDD (eg, cognition).
4) Treatments that can rapidly attenuate depressive symptoms.

Abbreviation: MDD, major depressive disorder.

genetic architecture when selecting antidepressant therapy is suggested by the heterogeneity in treatment response, tolerability, and safety of antidepressants among individuals.[6]

Over a dozen proprietary products that claim to offer improved therapeutic outcomes and/or cost-effectiveness when routinely administered into clinical practice are available globally. Notwithstanding the claims made and the scientific rationale supporting pharmacogenomic testing, current data do not support routine pharmacogenomic testing in MDD as either improving health outcomes and/or cost effectiveness.[7] Consequently, position statements from the American Psychiatric Association, Centers for Disease Control, and the US Food and Drug Administration (FDA) agree that pharmacogenomics testing should not be used routinely in clinical practice.[8] Nevertheless, there are reasons to believe that in the near future, integrating pharmacogenomic/transcriptomic data with other multimodality information (eg, neuroimaging) may be a routine part of the clinical assessment and decision support in the management of adults with MDD.[9]

Another key aspect of acceptability relates to drug-drug interactions (DDIs).[10] A pragmatic perspective to drug interactions with antidepressant therapy should also consider potential DDIs associated with the consumption of recreational marijuana and/or the use of Δ9-THC or cannabidiol (CBD).[11] Δ9-THC and CBD are known inhibitors of CYP3A4, with Δ9-THC also being an inhibitor of CYP2C9 and CBD also being an inhibitor of CYP2C19.[11] Marijuana inhalation also induces CYP1A1 and CYP1A2, an effect not seen with marijuana edibles.[11]

The need for greater efficacy across clinician- and patient-reported outcomes

Results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial indicate that with sequential therapeutic interventions, only approximately 10% to 15% of individuals will achieve remission after 2 prior antidepressant interventions.[12] In addition to suboptimal symptomatic outcomes in the short- and long-term, replicated and convergent evidence indicates that most adults with MDD do not achieve patient-reported outcomes (PROs). For example, most individuals with MDD, despite achieving symptomatic remission, do not achieve full functional recovery.[13] The implications for treatment acceptability and health outcomes of PROs in MDD were underscored by a post-hoc analysis of the STAR*D study, wherein investigators sought to determine the impact of a single multidimensional measure (ie, Individual Burden of Illness Index for Depression [IBI-D]) integrating symptoms functioning and quality of life.[14] When evaluating adults exiting Level 1 treatment in STAR*D remission, it was determined that IBI-D score alone was a powerful predictor of relapse over the ensuing 6 to 12 months.[14]

Treatments capable of attenuating critical dimension/domain-based outcomes in MDD

Select antidepressants are capable of improving measures of pain (eg, duloxetine, venlafaxine), while bupropion has demonstrated efficacy in smoking cessation and attention deficit hyperactivity disorder (ADHD).[15] Vortioxetine therapy can improve both objective and subjective measures of cognitive function in adults with MDD, an effect that is direct, independent, and clinically relevant.[16]

As a proxy of the need for multi-dimensional symptom relief in depression, it is amply documented that adults with MDD are frequently prescribed polypharmacy with combination antidepressants and adjunctive anxiolytics and hypnotics.[17] There has been a significant upward trajectory in the prescription of benzodiazepines, particularly in primary care, during the past 15 years.[17] It could be conjectured that the requirement for benzodiazepines in MDD reflects the unmet need of existing antidepressants to aggregate symptoms of anxiety, sleep disturbance, and dysphoria, and in some cases reflects the overactivating effect of antidepressants themselves.

It is a testable hypothesis, derived from the STAR*D study, that treatments that are capable of improving measures of cognition and/or motivation/anhedonia would be disproportionately better able to improve health outcomes/acceptability in MDD. In the interim, rational combinations of treatments in MDD should be selected and combined based on their ability to improve some of the foregoing features. Furthermore, results from individual patient meta-analyses indicate that pharmacotherapy and manualized-based cognitive behavioral therapies are not equally effective in MDD. This comes from the view that targeting select symptoms with pharmacotherapy is more effective than CBT at targeting symptoms commonly encountered (eg, psychic anxiety and fatigue).[18]

TABLE 2

Rapid-onset treatments for depression: treatments capable of offering clinically significant symptom mitigation within 24 hours

Nonpharmacological	Pharmacologic
• Electroconvulsive therapy (ECT) • Sleep deprivation	• Ketamine • Nitrous oxide • Brexanolone • Rapastinel ? • Buprenorphine-Samidorphan ? • Psychedelics (eg, Psilocybin, Ayahuasca)

The need for faster-onset treatments

During the past decade, several reviews have broadly aimed to ascertain the temporality of onset of action of antidepressants. Taken together, utilizing full sample data, it is now consistently observed that most adults who will eventually remit with a chosen antidepressant therapy begin to exhibit clinically observable changes (i.e., ≥20% improvement in depressive symptom severity from baseline) within 2 weeks of initiation of therapy.[19] The modest positive predictive value of early improvement is overshadowed by the robust negative predictive value of lack of symptomatic improvement within the first 2 weeks.[19]

Available evidence indicates that intravenous racemic ketamine and intranasal esketamine (recently FDA approved in March 2019 for treatment-resistant depression) can attenuate depressive symptomatology within 24 hours of treatment.[20] The rapid onset of action of ketamine therapy has not been demonstrated unequivocally with oral formulation.[21]

Historically, rapid-onset treatments in psychiatry have included sleep deprivation and, in some cases, electroconvulsive therapy (ECT).[22,23] The limitations of sleep deprivation and ECT are patient acceptability and high rates of relapse/recurrence with sleep restoration and/or the absence of continuation therapy.[22] Recently, the FDA approved brexanolone for postpartum depression; it exhibits robust and rapid antidepressant effects in women with postpartum depression within 1 to 2 days (***Table 2***).[24]

Conclusion

MDD is a severe disabling, often chronic disease associated with substantial loss of life. Notwithstanding the availability of proven multimodality antidepressant strategies, most individuals with MDD do not achieve the therapeutic objectives prioritized by patients, providers, and society. Treatment discovery and development in MDD is prioritizing unmet needs, particularly related to more effective treatments with rapid onset of action that can attenuate symptom severity, notably in dimensions that principally mediate health outcomes (eg, cognition, anhedonia).

REFERENCES

1. Organization WH, Others. Depression and Other Common Mental Disorders: Global Health Estimates. World Health Organization; 2017. https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf.
2. McIntyre RS, Lee Y. Cognition in major depressive disorder: a "Systemically Important Functional Index" (SIFI). *Curr Opin Psychiatry*. 2016;29(1):48-55.
3. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry*. 2015;72(4):334-341.
4. Goldstein BI, Carnethon MR, Matthews KA, et al. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2015;132(10):965-986.
5. Rosenblat JD, Lee Y, McIntyre RS. The effect of pharmacogenomic testing on response and remission rates in the acute treatment of major depressive disorder: A meta-analysis. *J Affect Disord*. 2018;241:484-491.
6. Fabbri C, Porcelli S, Serretti A. From pharmacogenetics to pharmacogenomics: the way toward the personalization of antidepressant treatment. *Can J Psychiatry*. 2014;59(2):62-75.
7. Rosenblat JD, Goldberg JF, McIntyre RS. Consumer warning for genetic tests claiming to predict response to medications: implications for psychiatry. *A J Psychiatry*. 2019;176(5):412-413.
8. Integrating Pharmacogenomics in Practice: One GIFT at a Time or a Package Deal? | | Blogs | CDC. https://blogs-origin.cdc.gov/genomics/2017/11/06/integrating-pharmacogenomics/. Accessed June 12, 2019.
9. McIntyre RS, Lee Y, Mansur RB. Treating to target in major depressive disorder: response to remission to functional recovery. *CNS Spectr*. 2015;20 Suppl 1:20-30; quiz 31.
10. Preskorn SH. Drug-drug Interactions in Psychiatric Practice, Part 1: Reasons, Importance, and Strategies to Avoid and Recognize Them. *J Psychiatr Pract*. 2018;24(4):261-268.
11. Rong C, Carmona NE, Lee YL, et al. Drug-drug interactions as a result of co-administering Δ9-THC and CBD with other psychotropic agents. *Expert Opin Drug Saf*. 2018;17(1):51-54.
12. 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.
13. Lee Y, Rosenblat JD, Lee J, et al. Efficacy of antidepressants on measures of workplace functioning in major depressive disorder: a systematic review. *J Affect Disord*. 2018;227:406-415.
14. Ishak WW, Greenberg JM, Cohen RM. Predicting relapse in major depressive disorder using patient-reported outcomes of depressive symptom severity, functioning, and quality of life in the Individual Burden of Illness Index for Depression (IBI-D). *J Affect Disord*. 2013;151(1):59-65.
15. Carroll FI, Blough BE, Mascarella SW, et al. Bupropion and bupropion analogs as treatments for CNS disorders. *Adv Pharmacol*. 2014;69:177-216.
16. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*. 2014;17(10):1557-1567.
17. Liu X, Ye W, Watson P, et al. Use of benzodiazepines, hypnotics, and anxiolytics in major depressive disorder: association with chronic pain diseases. *J Nerv Ment Dis*. 2010;198(8):544-550.
18. Boschloo L, Bekhuis E, Weitz ES, et al. The symptom-specific efficacy of antidepressant medication vs. cognitive behavioral therapy in the treatment of depression: results from an individual patient data meta-analysis. *World Psychiatry*. 2019;18(2):183-191.
19. Henssler J, Kurschus M, Franklin J, et al. Trajectories of acute Antidepressant efficacy: how long to wait for response? A systematic review and meta-analysis of long-term, placebo-controlled acute treatment trials. *J Clin Psychiatry*. 2018;79(3).
20. Mathew SJ, Zarate CA Jr. *Ketamine for Treatment-Resistant Depression: The First Decade of Progress*. Springer; 2016.
21. Rosenblat JD, Carvalho AF, Li M, et al. Oral Ketamine for Depression: a Systematic Review. *J Clin Psychiatry*. 2019;80(3).
22. Post RM, Uhde TW, Rubinow DR, et al. Differential time course of antidepressant effects after sleep deprivation, ECT, and carbamazepine: clinical and theoretical implications. *Psychiatry Res*. 1987;22(1):11-19.
23. McIntyre RS, Filteau M-J, Martin L, et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord*. 2014;156:1-7.
24. Kudlow P, Cha DS, Carvalho AF, et al. Nitric oxide and major depressive disorder: pathophysiology and treatment implications. *Curr Mol Med*. 2016;16(2):206-215.

Current PSYCHIATRY

Innovative Strategies for Treatment of Major Depressive Disorder: A Brief Review of Recent Developments

Michael E. Thase, MD

BOTTOM LINE: Innovative Strategies for Treatment of Major Depressive Disorder: A Brief Review of Recent Developments

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study demonstrated the need for alternate medications for patients who do not benefit from standard antidepressants. Innovative strategies that target novel mechanisms like ketamine, esketamine, brexanolone, and SAGE-217 may fill some of the unmet needs.

Introduction

After an exhilarating epoch of drug development that led to the introduction of more than a dozen second-generation antidepressants, the pace of discovery slowed to a virtual standstill; most of the "new" drugs introduced after 2000 were metabolites, stereoisomers, or reformulations of existing medications and virtually all targeted serotoninergic or noradrenergic neurotransmission.[1,2] As underscored by the results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[3] the need for alternate medications for patients who do not benefit from standard antidepressants remains unmet. In 2019, 2 antidepressants with truly novel mechanisms of action were approved by the US Food and Drug Administration (FDA). This article will summarize these and other recent developments in antidepressant therapy.

Ketamine, serendipity, and discovery of a paradigm-changing treatment for depression

Like the ground-breaking, serendipitous discoveries of the 1950s that led to the first-generation of antidepressants, a next generation of depression therapeutics may have begun with anecdotal observations during studies that employed a single, sub-anesthetic dose of intravenous (IV) ketamine as a pharmacological probe.[4] Ketamine is an old drug—first approved by the FDA in 1970—and its psychoactive effects are thought to result from potent, noncompetitive blockade of NMDA receptors.[5] Although safer than its ancestor phencyclidine (PCP), ketamine also has abuse potential because of its dissociative, euphorigenic, and psychotomimetic effects.[5] For these reasons, ketamine was used to investigate the role of glutamatergic neurotransmission in the pathophysiology and treatment of psychosis, which led to the unanticipated observation of rapid relief of depressive symptoms in several healthy volunteers "at risk" for psychosis. These effects were confirmed in smaller scale, double blind crossover studies of depressed patients[6-8] and, within a decade, there was broad replication that IV ketamine (0.4–0.6 mg/kg infused over 20 to 40 minutes) had antidepressant effects for 40% to 60% of patients with treatment-resistant depression (TRD).[9,10] As most ketamine responders will relapse within 4 to 7 days of a single infusion,[9,10] repeated dosing protocols were implemented such that frequency is gradually tapered from twice weekly to weekly to every other week.

Ketamine's novel mechanism of action, coupled with the rapidity of antidepressant effects, have generated considerable enthusiasm.[11,12] Potentially important clinical applications include inpatient units, where the cost of care generally exceeds $1000 day in most US settings. As IV ketamine therapy produces a rapid reduction in suicidal ideation,[13] use in emergency rooms coupled with "wrap around" crisis management also might reduce the need for hospitalization.

There are, however, many reasons to be cautious about the increasing use of ketamine.[14,15] Ketamine is a Schedule III controlled substance and there are medicolegal, ethical, and clinical concerns pertaining to its off-label use. Most ambulatory psychiatric practices are not well-suited to administer and monitor this drug: beyond the ketamine's psychoactive effects, relatively common transient side effects include cognitive impairment, nausea, sedation, tachycardia, and increased blood pressure, which require 1 to 2 hours of observation in a clinically supportive setting.[9] Guidelines have been proposed by an American Psychiatric Association Task Force to ensure the safety of IV ketamine therapy,[16] although in practice therapy is not regulated.

Arguably, the most ominous concerns about IV ketamine therapy pertain to the potential for tolerance of therapeutic effects and the possibility of later emerging

adverse effects. Indeed, people who abuse ketamine typically ingest progressively larger doses to "chase" the intoxicating effects. Complications such as neurotoxicity and a form of aseptic cystitis have been documented in some heavy users.[9,16] There are no data from well-controlled studies of longer courses of IV ketamine therapy, although anecdotal experiences from clinical practice suggest that many patients can receive ongoing therapy across months or even years without developing tolerance of antidepressant effects or adverse effects.

Esketamine: the first descendent of ketamine to receive FDA approval for TRD

As ketamine is a racemic compound, its S and R enantiomers were obvious candidates for commercial development. The S enantiomer, now called esketamine, was already in use as an anesthetic in some countries and antidepressant effects were observed both anecdotally[17] and in 1 small, well-controlled study.[18] Moreover, as esketamine is a more potent NMDA channel blocker than the R enantiomer, it was thought to be a good choice for research on other methods of drug delivery that could improve both the access to and convenience of therapy in ambulatory psychiatric settings. With this goal in mind, phase 2 and phase 3 studies of esketamine were conducted using a novel intranasal (IN) delivery device. Although IN drug delivery is generally not as predictable as IV administration, phase 1 studies suggested that adequate drug exposure could be achieved with IN administration of esketamine.[19]

The phase 3 program for IN esketamine (Spravato™) largely focused on 2 IN doses (56 mg and 84 mg) and was delimited to patients with TRD. The FDA approved IN esketamine (Spravato™) in early 2019.[20] The basis for approval included 2 positive pivotal trials,[21,22] as well as several positive phase 2 trials.[23,24] One of the pivotal studies required that patients begin a new antidepressant medication concurrent with starting IN esketamine (56–84 mg/day) or its masked placebo; participants received 2 doses per week for 4 weeks.[21] The antidepressant effects of IN esketamine were apparent 24 hours after the first dose and improvement was sustained across the double blind protocol. Although the magnitude of the effect was more modest than some had anticipated,[25] the numbers needed to treat for response and remission were both reasonably large (ranging from 5 to 7) and clinically meaningful. The side effects observed in the short term studies of IN esketamine were very similar to those observed with IV ketamine.[21,23,24] IN delivery is uniquely associated with an unpleasant taste (dysgeusia), which sometimes results in vomiting. The subjective intensity of dissociative and other "trippy" experiences also may be somewhat lower with IN delivery, which is consistent with the lower drug exposure compared with IV administration.

The second pivotal study used a relapse prevention paradigm, enrolling TRD patients who had responded to ≥4 weeks of adjunctive IN esketamine therapy (56 or 84 mg twice weekly).[22] After ensuring the stability of response and transition to weekly or every other week therapy, patients were randomly allocated to receive either ongoing IN esketamine therapy or were switched to masked placebo; all continued to take a standard antidepressant. Results were unequivocal: patients who received ongoing adjunctive IN esketamine had a significantly lower risk of relapse than those who were switched to IN placebo and this difference was evident within the first month of drug discontinuation. Importantly, aside from depressive relapse, there were no signs of drug withdrawal in the patients who were switched to placebo and no later emergent side effects in patients receiving ongoing IN esketamine therapy. Interestingly, the relative hazard of relapse following drug discontinuation was substantially greater among the subset of incompletely remitted patients compared with those who had fully remitted. To date, no comparative studies of IN esketamine have been conducted. There is obvious need for a head-to-head comparison with IV ketamine, particularly studies large enough to properly test safety, acceptability, noninferiority (ie, true therapeutic equivalence), and cost-effectiveness.

In contrast to the off-label use of IV ketamine, IN esketamine therapy in the United States will be carefully monitored according to a Risk Evaluation and Mitigation Strategy (REMS); the need for a REMS reflects the FDA's and the manufacturer's recognition that this is a new approach to therapeutics that warrants additional safeguards to ensure patient safety and responsible use of a controlled substance. Patients will be entered into a registry, only certified centers will provide IN esketamine therapy, the drug will not be sold at retail pharmacies, and patients will not have access to multiple doses of IN esketamine.

Other drugs that target glutamatergic neurotransmission

Several other drugs that modulate the NMDA receptor have not passed muster as antidepressants. Notably, phase 3 programs for 2 promising compounds that were being developed for IV therapy, lanecimine[25,26] and raspastinel,[27,28] were terminated because of insufficient evidence of efficacy. Several orally administered drugs that are known to antagonize glutamatergic neurotransmission, including riluzole, lamotrigine, and memantine, have also failed to show consistent antidepressant effects.[5]

Drugs that target endogenous opioid mechanisms

It has been suggested that the antidepressant effects of ketamine and esketamine may be differentiated from

other glutamatergic drugs by their effects on the endogenous opioid system.[24] Indeed, in a small experiment of IV ketamine responders, pretreatment with naltrexone blocked the antidepressant effects of IV ketamine, but not the dissociative effects.[29] There has been a longstanding interest in the relationships between the endogenous opiate system and dysphoria, despair, pleasure, and the anticipation of reward[30-32]; patent medications containing tincture of opium were once marketed to remedy emotional maladies. However, interest in the therapeutic potential of opiates has been suppressed by the strong potential for abuse and lethality of overdose; these concerns have grown even larger during the current epidemic of opiate abuse.

Recent pharmacologic developments that permit more selective modulation of opiate systems may provide a way forward.[32] For example, buprenorphine, which is a μ- and κ-opioid partial agonist with a better safety profile than conventional opioids, has shown some antidepressant effects in difficult-to-treat depression.[33,34] The investigational drug samidorphan, a potent μ-opioid antagonist, has been paired with buprenorphine to further dampen undesirable opiate effects and minimize abuse liability.[32] A sublingual proprietary formulation of this combination, called ALKS-5461, has been developed and, in a proof of concept study in TRD, the 2 mg/2 mg dose showed significant antidepressant effects as an adjunct to antidepressants.[35] A subsequent, large scale phase 3 program confirmed the overall safety of ALKS-5461, but the studies yielded inconsistent results on efficacy measures.[36-38] In early 2019, the FDA judged the evidence base to be insufficient for merit approval and suggested additional studies.

The evolving story of brexanolone: first member of a neurosteroid class of antidepressants?

Enthusiasm for research on the potential antidepressant effects of drugs that modulate gamma aminobutyric acid (GABA) neurotransmission was rekindled in the 1990s by recognition that GABA interneurons play an important role in dampening activation of excitatory amino acids such as glutamate.[39] Conventional GABAergic drugs are already widely used to treat anxiety and insomnia associated with depression, though many of these drugs are Schedule III controlled substances and none are actually approved for treatment of MDD. Recognition of the potential of the neurosteroid allopregnanolone, a metabolite of progesterone, to allosterically modulate extrasynaptic GABA-A receptors led to investigations of a proprietary, injectable formulation called brexanolone as an anticonvulsant.[40] Evidence that a precipitous drop in progesterone and allopregnanolone may be associated with the onset of depressive symptoms following childbirth,[41] coupled with emerging evidence on the safety of brexanolone, led to a series of studies in post-partum depression (PPD).[42-44] As both the proof of concept study[43] and a pair of phase 3 trials[44] showed significant antidepressant effects, brexanolone (Zulresso™) was approved by the FDA in early 2019 as the first treatment specifically indicated for PPD. By heritage, the drug is classified as a Schedule III controlled substance. Unlike all other psychiatric medications, brexanolone is administered via slow IV infusion across 60 hours (30 μg/kg/hour × 4 hours followed by 60 μg/kg/hour × 20 hours and 90 μg/kg/hour × 28 hours; the dose is tapered over the final 8 hours of therapy). The antidepressant effects of brexanolone are rapid and fully evident by the end of the 60 hour infusion; the magnitude of the drug effect was about a 20% difference (ie, 5 points) in symptom scores.[43,44] Currently, only a single infusion session is recommended and, in clinical trials, antidepressant effects were sustained across 4 weeks. Common side effects following a single IV infusion of brexanolone include sedation/somnolence, dry mouth, flushing, and loss of consciousness; about 4% of clinical trial participants with PPD discontinued brexanolone therapy because of intolerable side effects.[44] Because of the risk of loss of consciousness, monitoring by a health care professional is required throughout the infusion. Like esketamine, clinical use of brexanolone is regulated by a REMS, which includes a patient registry. Studies of an oral formulation of a related drug are under way, as are studies in other forms of depression.

Conclusions

In the past decade, therapeutic optimism about the prospects of truly novel antidepressants that target neural systems other than serotonin or norephinephrine has skyrocketed and, in 2019, 2 new antidepressants—IN esketamine for TRD and IV brexanolone for PDD—have been approved by the FDA. The wave of optimism and enthusiasm that such important discoveries must now be balanced by post-marketing research and sufficient clinical experience to understand the potential benefits and limitations of these new therapies. Nevertheless, it is fair to say that the broader concept of non-monoaminergic therapies has now been proved and the prospects for a third generation of antidepressant are better than ever before.

REFERENCES

1. Thase ME. New medications for treatment-resistant depression: a brief review of recent developments. *CNS Spectr*. 2017;22(S1):39-48.
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. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic,

perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994;51(3):199-214.
5. Murrough JW, Abdallah CG, Mathew SJ. Targeting glutamate signalling in depression: progress and prospects. *Nat Rev Drug Discov*. 2017;16(7): 472-486. PMID: 28303025
6. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47(4):351-354.
7. 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):856-64
8. 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.
9. Newport DJ, Carpenter LL, McDonald WM, et al; 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.
10. 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.
11. Duman RS. The Dazzling Promise of Ketamine. Cerebrum. 2018 Apr 1;2018. pii: cer-04-18. eCollection 2018 Mar-Apr.PMID: 30746033.
12. Krystal JH, Abdallah CG, Sanacora G, et al. Ketamine: A paradigm shift for depression research and treatment. *Neuron*. 2019;101(5):774-778.
13. 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*. 2018; 175(2):150-158.
14. Sisti D, Segal AG, Thase ME. Proceed with caution: off-label ketamine treatment for major depressive disorder. *Curr Psychiatry Rep*. 2014;16(12):527.
15. 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.
16. 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.
17. 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.
18. 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.
19. Kim J, Farchione T, Potter A, et al. Esketamine for treatment-resistant depression—first FDA-approved antidepressant in a new class. *N Engl J Med*. 2019 4;381(1):1-4.
20. Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. *Am J Psychiatry*. 2019;176(6):428-438.
21. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2019; Jun 5. [Epub ahead of print]
22. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2018; 75(2):139-148.
23. Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Am J Psychiatry*. 2018;175(7):620-630.
24. Schatzberg AF. A word to the wise about intranasal esketamine. *Am J Psychiatry*. 2019;176(6):422-424.
25. 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.
26. 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.
27. 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.
28. Preskorn S, Macaluso M, Mehra DO, et al; 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.
29. Williams NR, Heifets BD, Blasey C, et al. Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism. *Am J Psychiatry*. 2018;175(12):1205-1215.
30. 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.
31. Rantala MJ, Luoto S, Krams I, et al. Depression subtyping based on evolutionary psychiatry: proximate mechanisms and ultimate functions. *Brain Behav Immun*. 2017. pii: S0889-1591(17)30468-3. doi: 10.1016/j.bbi.2017.10.012.
32. Ehrich E, Turncliff R, Du Y, et al. Evaluation of opioid modulation in major depressive disorder. *Neuropsychopharmacology*. 2015;40(6): 1448-1455.
33. 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):e785-793. doi: 10.4088/JCP.13m08725.
34. 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.
35. 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.
36. Fava M, Thase ME, Trivedi MH, et al. Opioid system modulation with buprenorphine/samidorphan combination for major depressive disorder: two randomized controlled studies. *Mol Psychiatry*. 2019;24(1):176.
37. Thase ME, Stanford AD, Memisoglu A, et al. Results from a long-term open-label extension study of adjunctive buprenorphine/samidorphan combination in patients with major depressive disorder. *Neuropsychopharmacology*. 2019 Jun 29. doi: 10.1038/s41386-019-0451-3. [Epub ahead of print] PMID: 31254971.
38. Zajecka JM, Stanford AD, Memisoglu A, et al. Buprenorphine/samidorphan combination for the adjunctive treatment of major depressive disorder: results of a phase III clinical trial (FORWARD-3). *Neuropsychiatr Dis Treat*. 2019;15:795-808.
39. Krystal JH, Sanacora G, Blumberg H, et al. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. *Mol. Psychiatry*. 2002;7:S71-S80.
40. Martinez Botella G, Salituro FG, Harrison BL, et al. Neuroactive Steroids. 2. 3α-Hydroxy-3β-methyl-21-(4-cyano-1H-pyrazol-1′-yl)-19-nor-5β-pregnan-20-one (SAGE-217): a clinical next generation neuroactive steroid positive allosteric modulator of the (γ-aminobutyric acid)a receptor. *J Med Chem*. 2017;60(18):7810-7819.
41. Frieder A, Fersh M, Hainline R, et al. Pharmacotherapy of postpartum depression: current approaches and novel drug development. *CNS Drugs*. 2019;33(3):265-282.
42. Kanes SJ, Colquhoun H, Doherty J, et al. Open-label, proof-of-concept study of brexanolone in the treatment of severe postpartum depression. *Hum Psychopharmacol*. 2017;32(2). doi: 10.1002/hup.2576.
43. Kanes S, Colquhoun H, Gunduz-Bruce H, et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. *Lancet*. 2017;390(10093):480-489.
44. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet*. 2018;392(10152): 1058-1070.