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Not So Fast:
Recent Successes and Failures in Treating Depression

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Historically, rapid antidepressant effects within days to weeks were seen in response to electroconvulsive therapy (ECT). In contrast, antidepressant medications took 4 to 6 weeks to exert their antidepressant effects. However, trials with novel, rapid-acting antidepressant medications—including the glutamatergic modulator ketamine—have revolutionized our expectation of when antidepressant effects could be expected, that is, in a matter of hours or days instead of weeks or months. This paradigm shift has instilled hope in individuals struggling with depression, particularly treatment-resistant depression (TRD). The unmatched robustness of ketamine's effects, the notable recent FDA approval of its derivative esketamine for adults with TRD, and the recent approval of brexanolone for postpartum depression (PPD) underscore the first exemplars of a mechanistically novel and distinct antidepressant agent in decades. Yet, despite tremendous progress, challenges have arisen in our investigation of many promising, novel, and rapid-acting (as well as non–rapid-acting) antidepressant interventions for depression. Here, we briefly assess some of these recent successes and setbacks.

Ketamine

Initial preclinical studies in the 1990s implicated the glutamatergic system in the etiology of mood disorders.[1] The first small clinical study of intravenous subanesthetic-dose (0.5 mg/kg) ketamine, administered over 40 minutes, showed that this agent had unusually rapid and robust antidepressant effects.[2] Since then, multiple double-blind, placebo-controlled, randomized trials have established ketamine's antidepressant efficacy for TRD, both in individuals with major depressive disorder (MDD)[3,4] and in those with bipolar depression.[5,6] Meta-analyses subsequently corroborated these findings.[7–11] A single ketamine infusion was also found to have significant and rapid (1 to 4 hours) antisuicidal ideation effects.[12–15] Furthermore, while the robust antidepressant effects of subanesthetic-dose ketamine were found to be transient, researchers were able to successfully prolong these effects with repeated infusions.[16–18] These groundbreaking findings led to the development of intranasal esketamine, the stereoisomer derived from racemic ketamine. Positive phase 3 clinical trials established its efficacy,[19–21] which led to the recent (March 2019) FDA approval of intranasal esketamine for adults with TRD.[22]

Despite these advances, ketamine's underlying mechanisms of action remain largely unknown. The prevailing hypothesis is one of direct and indirect antagonism at the *N*-methyl-D-aspartate receptor (NMDAR) as well as AMPA throughput modulation.[23,24] These converging mechanisms appear to induce rapid and sustained changes in synaptic plasticity that result in increased synaptic spine turnover that, in turn, propagates ketamine's antidepressant-like effects over time.[25] Studies suggest that a cascade of several mechanisms triggered by ketamine's unique pharmacodynamic profile might be critical to its antidepressant effects.[23]

As our theoretical understanding of ketamine's mechanisms of action grew, several preclinical candidate drugs whose mechanistic processes were purported to overlap with those of ketamine (eg, lanicemine, GLYX-13, and 4-chlorokynurenine [4-Cl-KYN]) were explored to investigate whether these would mimic ketamine's rapid and robust antidepressant properties while avoiding its dissociative and psychotomimetic side effects. Although some promising agents emerged, other early phase 2 or 3 clinical studies failed to show clinical efficacy.[26] While a comprehensive review of this topic is beyond the scope of this article, below we highlight a handful of candidate examples. For additional information, the interested reader is referred to recent review articles on this subject.[23,27]

"Ketamine-Like" Agents

Lanicemine. Lanicemine (AZD6765) is a low-trapping, noncompetitive NMDAR channel blocker whose mechanism of action was thought to be similar to that of ketamine but without ketamine's dissociative or psychotomimetic side effects. Though early clinical studies were promising,[28] a subsequent 3-week, placebo-controlled trial of repeated-dose adjunctive lanicemine found that this agent had antidepressant effects but that these were not rapid.[29] A larger, 6-week, phase 2b study of adjunctive repeated-dose (50 mg and 100 mg) lanicemine then found that this agent did not separate from placebo on primary endpoint measures[30]; clinical development of the compound was terminated due to lack of efficacy.[30]

GLYX-13. GLYX-13 is an intravenously administered tetrapeptide whose mechanism of action has yet to be fully elucidated. However, recent findings suggest its mechanism of action is pharmacologically unique and may involve NMDAR activation via a novel binding domain, even in the absence of glycine.[31] Building on several initially promising preclinical studies showing mechanistic overlap with ketamine,[32] phase 1 and 2 clinical trials found that GLYX-13 was well tolerated and exhibited rapid-acting lasting antidepressant properties in TRD participants without producing psychotomimetic effects.[33] However, GLYX-13 failed to meet primary or secondary endpoints in subsequent large phase 3 trials.[34] Several ongoing studies are assessing the long-term antidepressant properties of GLYX-13 in individuals with MDD—both as adjunctive treatment and as monotherapy.

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4-Chlorokynurenine. 4-Cl-KYN is a prodrug of an NMDAR glycine B site antagonist. In preclinical models, 4-Cl-KYN induced rapid and sustained antidepressant effects without ketamine-related side effects,[35] suggesting that directly targeting the glycine B site with an antagonist might be a viable antidepressant strategy. However, a recent phase 2, placebo-controlled, crossover study evaluating a 2-week course of 4-Cl-KYN monotherapy in 19 TRD participants found that this agent failed to improve participants' overall depressive symptomatology, nor did it engage the primary target in brain.[36] A multisite study in TRD is currently underway.

Other Novel Interventions for Depression

Brexanolone (SAGE-547). In March 2019, the FDA approved brexanolone (SAGE-547), the first drug specifically indicated for PPD. Brexanolone is a synthetic formulation of allopregnanolone and a known positive allosteric modulator of γ aminobutyric acid type A ($GABA_A$) receptor function.[37] In 2 large, phase 3 trials, 138 women with moderate to severe PPD were randomly assigned to a single 60-hour infusion of either brexanolone (60 or 90 μg/kg/h) or placebo. Mean reductions in depression rating scale scores from baseline were greater in the group receiving brexanolone versus placebo, and the proportion of participants achieving remission was also significantly higher for the brexanolone groups.[38,39]

Relatedly, SAGE-217 is an analogue of allopregnanolone similar to brexanolone but intended for once-daily oral dosing. A previous phase 3 trial found that SAGE-217 met primary and secondary endpoints for PPD,[40] and an earlier, double-blind, phase 2 trial found that daily administration of SAGE-217 reduced depressive symptoms at day 15.[41] However, in a recent phase 3 trial in MDD, SAGE-217 was not superior to placebo at its primary endpoint at day 15.[42]

Theta burst stimulation and electroconvulsive therapy. Device-based treatments are another source of rapid antidepressant effects. In August 2018, the FDA approved intermittent theta burst stimulation (iTBS). The iTBS protocol can be delivered in 3 minutes (versus 37 minutes for the conventional repetitive transcranial magnetic stimulation [rTMS] protocol) and has been shown to facilitate cortical excitability.[43] In a multicenter clinical trial of 400 participants randomized to receive either iTBS or standard 10 Hz rTMS, iTBS had equivalent antidepressant efficacy to rTMS.[44] Furthermore, a recent, open study[45] of 22 TRD participants demonstrated the feasibility of using an accelerated high-dose resting-state functional connectivity MRI-guided iTBS protocol for TRD. Ongoing studies are investigating ways to shorten the time of each treatment session as well as accelerate response.[46]

Another notable development in this area is that the FDA reclassified ECT in December 2018, downgrading its risk category from Class III (high risk) to Class II (moderate risk). Despite ECT's superior clinical efficacy—it has the largest effect size of all available treatments for depression[47]—its use is both limited and declining,[48] typically because of its potential to cause adverse cognitive effects. Alternative approaches and novel technologies may soon allow for more individualized and selective targeting with ECT, including the use of multichannel stimulation systems and computational electric field models to characterize intracranial current flow.

Conclusion

The evidence reviewed above suggests that a complex drug like ketamine, though responsible for a considerable therapeutic breakthrough, may have a somewhat unique pharmacologic profile that is difficult to reproduce. The recent failure of several novel therapies for depression deserves thorough reflection by the scientific community; in particular, the importance of bench-to-bedside translational paradigms that lead from basic science research to clinical trials deserves scrutiny. Perhaps attempts to "sanitize" the side effect profile of ketamine-like agents could serve as a learning example for the entire field, helping to reconceptualize the challenging and complex process that drug discovery in psychiatry is facing. In this context, the scientific community might reconsider its traditional path of translating animal models for novel drug testing and re-examine ways to address particular study design and phase-to-phase feasibility challenges when designing or testing novel therapeutics.

Despite these setbacks, we wish to stress that the situation is not bleak. Indeed, the discovery of ketamine's rapid antidepressant effects ushered in a new era of paradigm-shifting research focused on developing or repurposing new antidepressant therapies capable of working within hours or days versus weeks or months. Most notably, the recent FDA approval of esketamine for TRD and brexanolone for PPD marks the first time in 50 years that 2 antidepressants with distinct novel mechanisms of action have reached the market. Along these lines, in 2018 the FDA also cleared the iTBS protocol. The approval of 3 new treatments—esketamine, brexanolone, and theta burst stimulation—for the treatment of depression over the course of a single year is a singular achievement that highlights the possibility of developing urgently needed next-generation treatments based on an improved understanding of the precise mechanistic processes underlying their therapeutic properties. As a field, we continue to learn from both our successes and our failures to enhance study design and move promising agents forward from bench to bedside.

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Potential conflicts of interest: **Dr Zarate** is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (*R,S*)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorders. He has assigned his patent rights to the US government but will share a percentage of any royalties that may be received by the government. **Drs Deng** and **Lisanby** have an issued patent on TMS technology, assigned to Columbia University, not licensed, and with no renumeration. **Dr Lisanby** has received grant support from the Brain and Behavior Research Foundation, the Stanley Medical Research Foundation, Neosync, Nexstim, National Institutes of Health, and Brainsway. **Drs Kadriu** and **Kraus** and **Ms Henter** have no conflict of interest to disclose, financial or otherwise.

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