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Glutamate modulators and beyond: A neuroscience revolution in the making

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Since 2018, significant advances have been made to treat major depression and treatment-resistant major depression (TRD). These include the FDA approvals of esketamine for TRD in adults with major depression as well as in adults with suicidal ideation or behavior, of brexanolone for postpartum depression, and of iTMS for major depression.

This remarkable progress is particularly exciting because, until racemic (*R,S*)-ketamine was introduced for clinical antidepressant use in the 2000s, the development of novel treatments for depression had stalled despite many decades of research. Most “new” antidepressants worked on similar mechanisms as their predecessors—predominantly affecting the monoaminergic system—but did not noticeably improve remission rates or have a more rapid onset of action. Indeed, not until the glutamatergic system began to be studied in earnest was the stage set for developing next-generation antidepressants (Skolnick et al., 2009).

In the 2000s, under careful testing conditions, a single intravenous (*R,S*)-ketamine infusion was demonstrated to have rapid (within hours), robust, and relatively sustained (one to two weeks) antidepressant efficacy in major depression, TRD, and bipolar depression. In subsequent studies, both single and repeated administration of (*R,S*)-ketamine and esketamine, ketamine’s *S*-enantiomer, had rapid and robust antidepressant effects in TRD patients. Recent guidelines and reviews provide a framework for the ethical, clinical use of ketamine in the community (McIntyre et al., 2021).

As noted earlier, decades-long efforts to develop antidepressants had until recently led to few FDA approvals. Although the reasons for these failures are multifactorial (reviewed in (Hutson et al., 2017)), it is clear that drug development strategies were largely unsuccessful until ketamine’s rapid antidepressant efficacy refocused these efforts to target the glutamatergic and GABA-ergic systems. Nevertheless, several challenges have complicated the clinical use of ketamine and esketamine; these include dissociative

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Declaration of Competing 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 dehydroxylated 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 post-traumatic stress disorders. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government.

side effects and misuse potential as well as insufficient data regarding their long-term health effects. In this context, the field has sought to back-translate ketamine from the clinic to the bench in order to decipher its mechanistic processes. On the preclinical and clinical fronts, such work has helped identify numerous agents in different stages of investigation, including broad glutamatergic modulators ((*R,S*)-ketamine, esketamine, (*R*)-ketamine, (2*R*,6*R*)-hydroxynorketamine, dextromethorphan, deudextromethorphan, axsome, dextromethadone, nitrous oxide, AZD6765, CLE100, AGN-241751); glycine site modulators (D-cycloserine, NRX-101, rapastinel, apimostinel, sarcosine, 4-chlorokynurenine); subunit (NR2B)-specific NMDAR antagonists (eliprodil, traxoprodil, rislenemdaz); mGluR modulators (basimglurant, AZD2066, RG1578, TS-161); and mTORC1 activators (reviewed in (Henter et al., 2021)).

Notably, this surge in the number of clinical studies has not always yielded viable candidate drugs. For example, although (*R,S*)-ketamine is an NMDAR antagonist, other NMDAR antagonists do not appear to share ketamine's unique characteristics, including its rapid (within hours) onset of antidepressant effects, the sustained duration of these effects, and its broad therapeutic properties. Possible explanations for the lack of efficacy of these other NMDAR antagonists include differences in NMDAR subunit selectively, a need to combine with other mechanisms besides NMDAR blockade, and preclinical models that are not directly translatable to human disease. In short, our understanding of what makes ketamine unique is still in its infancy, and our ability to modify or develop agents that echo its properties has proven elusive.

The field is also vigorously pursuing studies that dissect the cellular and molecular mechanisms thought to be implicated in ketamine's immediate and sustained antidepressant effects. One avenue of interest is biomarker studies; these examine a range of translational biomarkers, including those drawn from imaging and electrophysiological studies, sleep and circadian rhythms, and endocrine function as well as metabolic, immune, (epi)genetic, and neurotrophic biomarkers related to ketamine response (Kadriu et al., 2020). For instance, altered cortical excitation/inhibition has been implicated in both major depression and in ketamine's mechanism of action (Fagerholm et al., 2021). Recent mechanistic studies in humans have also explored the role of mTORC1 and opioid receptors (McIntyre et al., 2021). As regards addiction, a recent report suggests that (*R,S*)-ketamine's abuse liability in humans stems primarily from the pharmacological effects of its (*S*)-enantiomer (Bonaventura et al., 2021), a finding with enormous implications for putative next-generation treatments based on ketamine's enantiomers (*R*- and *S*-ketamine) and its metabolites (Gould et al., 2019). Interestingly, it was recently proposed that focal glutamatergic hyperactivity in the ventral anterior cingulate cortex (vACC) may lead to global reductions in monoaminergic activity, resulting in depressive symptoms. Under this paradigm, monoaminergic antidepressant efficacy—such as that associated with SSRIs—would restore this global reduction over time, whereas rapid-acting antidepressants (e.g., ketamine/esketamine, deep brain stimulation (DBS), GABA type A ($GABA_A$) receptor modulators, etc) would do so in a more rapid and immediate fashion by attenuating vACC hyperactivity (Artigas, 2021).

The paradigm-shifting nature of ketamine research—with its goal of antidepressant effects that manifest within hours instead of over weeks or months—has also spurred investigators to study other candidate drugs with potentially rapid antidepressant effects, including serotonergic psychedelics (SPs). Although SPs and ketamine appear to have different initial targets, increasing evidence suggests a potentially shared mechanism whereby both may produce rapid neuroplastic effects in a glutamatergic activity-dependent manner (Kadriu et al., 2021). Definitive studies are also currently underway for brexanolone, which recently received FDA approval to treat postpartum depression. As with SPs, the initial target for ketamine and brexanolone might be distinct, but downstream commonalities on glutamatergic systems may come into play. Presently, however, a common mechanism linking SPs, brexanolone, and ketamine remains largely speculative.

For many years, few advances were made in developing improved pharmacological therapies for depression. In contrast, the propulsive progress of the past 20 years is reason for considerable hope. While many challenges certainly remain, this era of progress has already been marked by significant advances in both the preclinical and clinical space. TRD patients now have several unique and, more importantly, different therapeutics to try if conventional antidepressants fail to work. As a field, we also now have a model drug and other rapid-acting antidepressants to use as blueprints in future drug development efforts. Together, these advances will help us move beyond our current challenges, ultimately resulting in improved therapeutics for our patients.

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