Have Effective Antidepressants Finally Arrived? Developments in Major Depressive Disorder Therapy

Michael E. Thase, MD

Major depressive disorder (MDD) is the leading cause of disability among individuals aged 15 to 44 worldwide and poses a substantial challenge to health care providers.[1] Among the greatest unmet needs in MDD is a lack of effective pharmacotherapies for patients who do not respond to first- and second-line antidepressant medications. Medications that have a faster onset of benefit and address some of the more difficult to treat symptoms, such as anhedonia and suicidal ideation, would also address unmet needs.

Over the last 40 years, the response rate to antidepressants in randomized controlled trials has stagnated between 52% and 54%.[2] Meanwhile, between 2015 and 2023, the estimated rate of lifetime depression has surged from 19.6% to a record high of 29.0%.[3] Extrapolating from clinical trial data, one can surmise that the specific effects of antidepressants convey only about a 10%–20% advantage over the so called nonspecific factors of treatment, including the placebo effect.[4] Could it be that a large minority of depressed people may have illnesses that are not addressed by drugs that target serotonergic or noradrenergic neurotransmission? Unfortunately, the search for alternate pharmacologic targets that might relieve depressive symptoms has been elusive, and in the 1990s and early 2000s, researchers noted that novel compounds that targeted a variety of other putative mechanisms of action, including corticotropin-releasing factor antagonists, substance P antagonists, nicotinic partial agonists, and triple reuptake inhibitors, all had little to no utility in alleviating the burdensome symptoms characteristic of MDD.[5]

After decades of muted progress, optimism regarding the future of MDD therapy rose after scientists serendipitously uncovered the antidepressant effects of intravenous ketamine—a dissociative anesthetic and *N*-methyl-D-aspartate (NMDA) receptor antagonist. In a small crossover study of patients with depression, researchers noted that administration of 0.5 mg/kg ketamine resulted in a sustained, 3-day reduction of depressive symptoms in recipients with MDD.[6] Beyond "proving the concept" that a drug that directly addressed glutamatergic signaling could treat MDD, the discovery of ketamine's antidepressant effects inspired the search for related newer medications, such as *S*-ketamine (esketamine), which was developed for intranasal administration and approved by the US Food and Drug Administration (FDA) as an adjunctive strategy for treatment-resistant depression in 2019.[7] Notably, the relatively rapid effects of intravenous ketamine and intranasal esketamine have shown promise in MDD patients with acute suicidal ideation, which became the second FDA-approved indication for esketamine in 2020.[8] Despite such promise, the potential benefits of ketamine and esketamine must be balanced in practice against cost and the potential of side effects such as sedation and dissociation. These drugs also indirectly interact with opioid systems and are classified as Schedule III controlled substances, with some potential for abuse.[9]

Alternative, orally administered NMDA antagonists unrelated to ketamine have also demonstrated considerable promise in recently concluded, late-stage clinical trials. Researchers evaluating an extended-release combination of bupropion (105 mg) and dextromethorphan (45 mg) administered twice daily found that recipients of the formulation experienced an 11.1-point decline in MADRS total score at week 2; participants assigned placebo experienced a 7.7-point decline.[10] Another cohort of patients with treatment-resistant depression experienced rapid, robust, and sustained decreases in depressive symptoms when treated with adjunctive esmethadone at 25 mg and 50 mg doses in a phase 2a clinical trial.[11] Although this success was not replicated in a subsequent phase 3 trial, secondary analyses suggest that signal detection was ruined by too many sites having a high placebo

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response.[12] Another pair of phase 3 studies are ongoing, which will help to determine if the promising findings from the phase 2a trial are replicable.[12]

Neurosteroids, such as brexanolone and zuranolone, appear to represent another class of antidepressants. These drugs appear to modulate GABA neurotransmission, which has long been known to be a pathway for drugs that are used to treat insomnia and anxiety. However, unlike benzodiazepines, which carry the risk of tolerance of therapeutic effects and dependence, brexanolone does not lead to symptoms of "drug liking," with researchers noting no signs of withdrawal, misuse, or abuse during clinical trials.[13,14] Intravenous brexanolone became the first member of this class of drugs to be approved by the FDA for treatment of a depressive disorder in 2019. In a pair of multicenter, double-blind, randomized, placebo-controlled phase 3 trials of women with postpartum episodes of MDD, researchers observed that a single, intravenous injection of brexanolone (60 µg/kg per hour, 90 µg/kg per hour) resulted in rapid, clinically meaningful reductions in depression, as quantified by the Hamilton Depression Rating Scale (HDRS) at 60 hours, which persisted for up to 1 month after treatment.[15] A second member of the class, zuranolone, is being studied across the full range of MDD. Across 4 clinical trials, study investigators have validated zuranolone at 30 mg and 50 mg doses and have similarly observed significant changes from baseline in HDRS-17 total scores over a period of 15 days.[16] One interesting ideal being explored in the zuranolone phase 3 program is whether this class of drugs can be usefully implemented with "intermittent" treatment, ie, only 1–3 two-week courses of treatment per year.

After nearly 50 years of legal injunctions against their use, psychedelic drugs have attracted interest among researchers seeking alternative antidepressants. Findings from small, uncontrolled studies in patients with treatment-resistant depression and terminal cancer suggest that psilocybin, derived from mushrooms, can result in significant, sustained antidepressant effects.[17,18] Although the margin with which psilocybin outperformed the selective serotonin reuptake inhibitor escitalopram was not statistically significant at the end of one phase 2 trial, other data support psilocybin's ability to alleviate symptoms rapidly; the psychedelic remains under investigation for its benefits in treatment-resistant depression.[19,20]

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Faculty Affiliations: Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia.

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