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Importance of achieving rapid treatment response in major depressive disorder

Gustavo Alva

ATP Clinical Research, Costa Mesa, CA, USA

Abstract

Major depressive disorder (MDD) is a leading contributor to disability worldwide and is associated with increased morbidity and mortality. Current pharmacologic treatment options may be ineffective for some patients and can pose several limitations and challenges, including suboptimal response and slow onset of action. Many of these therapies can take 6 to 8 weeks for patients to achieve response and 12 weeks or longer to demonstrate full clinical benefit. Delays in depressive symptom resolution are associated with poor symptomatic and functional outcomes, decreased quality of life, and increased burden on the healthcare system. Achieving response and remission of symptoms soon after diagnosis and treatment is associated with lower rates of relapse and a greater likelihood of functional recovery. An unmet need exists for innovative treatments that offer rapid and sustained effects. This editorial discusses the benefits of rapid improvement in depressive symptoms with available and investigational agents for patients with MDD.

Editorial

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Corresponding author:
Gustavo Alva
Email: galva@atpcr.com

Introduction

For patients living with major depressive disorder (MDD), delays in treatment response can lead to nonadherence, multiple failed therapies, and negative health-related quality of life (HRQoL) outcomes.[1,2] Current guidelines recommend starting pharmacologic antidepressant therapy (ADT) or psychotherapy as an initial treatment option for patients with mild-to-moderate MDD and both pharmacotherapy and psychotherapy for those with moderate-to-severe MDD.[3,4] Standard-of-care (SOC) ADTs (eg, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors) have several treatment-limiting side effects in some patients, including sexual dysfunction, weight gain, and disturbed sleep, which may contribute to nonadherence.[5-8] Accordingly, guidelines recommend a "start low, go slow" approach to dosing ADTs when treating patients with MDD; since most SOC ADTs typically take several weeks to achieve maximal efficacy, patients are encouraged to continue these ADTs for 6 to 8 weeks before increasing the dose or switching to another agent.[3,9] As many as ≥50% of patients may not respond (as measured by ≥50% reduction in 17-item Hamilton Rating Scale for Depression [HAMD-17] total score, a tool often used in clinical trials to assess depressive symptoms) to their initial ADT and will need changes to therapy—leading to a longer time to achieve therapeutic benefit, and in some instances, chronic treatment for sustained benefit.[2] Patients in the STAR*D study who required >1 treatment step were less likely to achieve remission (HAMD-17 total score ≤7) and more likely to relapse than those who responded to their first ADT.[2] A rapid response to treatment is associated with long-term remission, whereas patients with delayed response were more likely to experience residual symptoms, including anxiety, sleep disturbances, pain, and decreased concentration.[6,7] To prevent relapse, close attention should be placed on patients who require a relatively long time to achieve remission.[10] Together, protracted treatment with SOC ADTs, residual symptoms, and delayed remission can lead to negative impacts on HRQoL, with ≥50% of patients facing severely impaired HRQoL after trying multiple lines of therapy.[1,11] In contrast, patients who experience a shorter time to response or remission can experience fewer mental, physical, and financial hardships compared with those who experience a longer time to response or remission.[6,12] The negative impacts of a relatively long time-to-effect with SOC ADTs underscore the need for novel therapies that can provide patients with MDD (including those experiencing suicidal ideation or behavior) improvements in depressive symptoms that are rapid (ie, within 1 week) and sustained.[13]

Currently available interventions with rapid and sustained improvement

Electroconvulsive therapy (ECT), which involves applying electrical stimulation to a patient's brain to produce a seizure, is an FDA-approved nonpharmacologic intervention associated with rapid and sustained effects in patients with severe treatment-resistant depression (TRD) and clinical emergencies that require rapid improvements in depressive symptoms (Table 1).[14,15]

Table 1. Currently available and investigational treatments with rapid and sustained response in patients with MDD

Agent	Class	Indication	Earliest Time to Efficacy	Warnings and Precautions	Supporting References
Approved Nonpharmacologic Therapies					
ECT	Nonpharmacologic	Patients aged ≥13 years with severe MDE associated with MDD	Week 1	Headache, memory complaints, and elevations in heart rate and blood pressure	Husain 2004[16]
TMS	Nonpharmacologic	Adults with MDD with prior failed ADT	Week 1	Headache and scalp pain	Wang 2017[17]
SAINT	Nonpharmacologic	Adults with MDD with prior failed ADT	Week 1	Headache	Cole 2022[18]
Approved Pharmacologic Therapies					
Brexanolone	$GABA_AR$ PAM NAS	Patients aged ≥15 years with PPD	Within 24 hours	Somnolence, dizziness, headache, and sedation	Kanes 2017[19] Meltzer-Brody 2018[20]
Esketamine	NMDA receptor antagonist	For use in conjunction with oral ADT in adults with TRD For use in conjunction with oral ADT in adults with MDD with acute suicidal ideation or behavior	Within 24 hours Within 4 hours	Dissociative symptoms, sedation, dizziness, and abuse potential	Marwaha 2023[21]
Ketamine	NMDA receptor antagonist	Off-label use for treatment-resistant MDD	Within 24 hours	Dissociative symptoms, sedation, dizziness, transient blood pressure changes, and abuse potential	Murrough 2013[22]
Dextromethorphan-bupropion	NMDA receptor antagonist	Adults with MDD	Week 1	Dizziness, nausea, headache, diarrhea, somnolence, and dry mouth	Iosifescu 2022[23]
Aripiprazole	Second-generation antipsychotic	Adjunctive therapy in adults with MDD	Week 1	Akathisia and weight gain	Berman 2007[24]
Brexpiprazole	Second-generation antipsychotic	Adjunctive therapy in adults with MDD	Week 1	Akathisia and weight gain	Thase 2015[25]
Quetiapine XR	Second-generation antipsychotic	Adjunctive therapy in adults with MDD	Week 1	Dry mouth, somnolence, sedation, and weight gain	Bauer 2009[26]; El-Khalili 2010[27]
Investigational Therapies					
Psilocybin	$5\text{-}HT_{2A}$ receptor agonist	Adults with MDD	Within 24 hours	Emotional effects, headache, nausea, feeling jittery, vomiting, palpitations, and sleep disorder	Davis 2021[28]
Esmethadone (REL-1017)	NMDA receptor antagonist	Adjunctive therapy in adults with MDD	Day 4	Headache, constipation, nausea, and somnolence	Marwaha 2023[21]
Zuranolone	$GABA_AR$ PAM NAS	Adults with MDD and PPD	Day 2 or 3	Somnolence, dizziness, headache, and sedation	Gunduz-Bruce 2019[29] Clayton 2022[30] Deliagannidis[31]

Abbreviations: $5\text{-}HT_{2A}$, 5-hydroxytryptamine type 2A; ADT, antidepressant therapy; ECT, electroconvulsive therapy; $GABA_AR$, gamma-aminobutyric acid type A receptor; MDD, major depressive disorder; MDE, major depressive episode; NAS, neuroactive steroid; NMDA, N-methyl-D-aspartate; PAM, positive allosteric modulator; PPD, postpartum depression; SAINT, Stanford accelerated intelligent neuromodulation therapy; TMS, transcranial magnetic stimulation; TRD, treatment-resistant depression; XR, extended release.

ECT is believed to treat depression by inducing neurogenesis and increasing neurotrophic signaling and is considered an effective treatment option for patients with MDD. Transcranial magnetic stimulation (TMS) is another FDA-approved, rapid-acting nonpharmacologic therapy to treat adults with MDD for whom prior ADTs failed.[32,33] TMS noninvasively uses a strong pulsated magnetic field to stimulate a specific area of the cerebral cortex, leading to increased neural activity in the region.[34] Although its precise mechanism of action is unclear, TMS is hypothesized to address inhibitory-excitatory imbalance between gamma-aminobutyric acid (GABA) and glutamate neurotransmission. Another form of TMS, the Stanford accelerated intelligent neuromodulation therapy, also received FDA approval to treat MDD in adults for whom prior ADTs failed.[18] Both ECT and TMS approaches provide rapid improvements in depressive symptoms within 1 week that may be sustained for several weeks.[16-18,35] However, a limitation of these approaches is that they require administration by trained providers at specialized treatment locations, in some cases over multiple sessions.

Several pharmacotherapies with rapid and sustained effects are approved or used off-label as monotherapies or adjunct therapies for the treatment of MDD and other depressive disorders.

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Ketamine, esketamine, and dextromethorphan-bupropion are thought to act as N-methyl-D-aspartate (NMDA) receptor antagonists and elicit antidepressant effects through modulation of glutamate signaling (Table 1). These agents demonstrate rapid effects in as little as an hour, with improvements in depressive symptoms sustained up to 6 weeks.[21-23] However, ketamine and esketamine are limited by dissociative side effects and the potential for abuse, as well as the need for in-clinic visits to administer treatments.[21] Additionally, dextromethorphan is administered with bupropion, a potent cytochrome P450 2D6 inhibitor that increases the risk for drug-drug interactions and is associated with an increased risk of seizures.[36] The antidepressant activity of glutamatergic drugs supports the hypothesis that excitation-inhibition signaling in the brain is dysregulated in depression, suggesting that modulation of excitatory (glutamate) and inhibitory (GABA) signaling is a promising target for novel ADTs. Brexanolone, a neuroactive steroid and positive allosteric modulator (PAM) of $GABA_A$ receptors ($GABA_A$Rs), is the only FDA-approved pharmacologic therapy for postpartum depression (PPD) and elicits rapid improvements in depressive symptoms in as early as 24 hours, but is limited by the need for a 60-hour intravenous infusion in a clinical setting.[20,21,37]

Dopamine and serotonin partial agonist antipsychotics, aripiprazole and brexpiprazole, also provide rapid and sustained benefits, but their use is limited by the potential for psychomotor side effects such as akathisia.[24,25] Quetiapine is a norepinephrine reuptake inhibitor antipsychotic used as an adjunct to SOC ADTs that also demonstrates rapid and sustained benefits, but is associated with side effects (eg, weight gain) that may be treatment limiting.[26,27] While there are available therapies that, alone or in combination with SOC ADTs, may help to achieve rapid relief from depressive symptoms, their limitations, both practical and therapeutic, indicate a need for newer therapies.

Investigational pharmacologic interventions with the potential for rapid and sustained improvement

Psychedelics have emerged as a promising class of investigational therapies with the potential for rapid and sustained improvements in depressive symptoms for patients with MDD (Table 1). Psilocybin, a 5-hydroxy-tryptamine type 2A receptor agonist, is a psychedelic compound that can improve depressive symptoms in conjunction with psychotherapy, with studies demonstrating effects 1 week postdose that were sustained through 8 weeks without maintenance dosing.[21,28] However, some patients treated with psilocybin have experienced emotional effects, including anxiousness, fear, and other emotional distress during treatment sessions, and use of psilocybin is limited by the need to receive treatment in a clinical setting and remain under supervision for several hours.[21,28,38] Esmethadone, a novel NMDA receptor antagonist, can provide improvements in as little as 4 days of treatment in patients for whom up to 3 ADTs failed, but its long-term efficacy is unknown.[21]

Modulation of GABAergic signaling is an evolving approach to treat MDD among investigational therapies (Table 1). Zuranolone is a $GABA_A$R PAM and neuroactive steroid that is thought to upregulate $GABA_A$R expression and enhance GABAergic signaling via synaptic and extrasynaptic $GABA_A$Rs; zuranolone is currently in clinical development as an oral, once-daily, 14-day treatment course for MDD and PPD in adults.[29,30,39-41] Targeting both synaptic and extrasynaptic $GABA_A$Rs distinguishes zuranolone from other GABAergic drugs, such as benzodiazepines, which only target synaptic receptors.[39] Across several clinical trials, patients with MDD or PPD treated with zuranolone experienced rapid improvements in depressive symptoms that were sustained for several weeks beyond the 14-day treatment course; the most common side effects included headache, dizziness, somnolence, and sedation, which were mostly mild or moderate in severity.[29,31,42] Interim results from an ongoing, open-label, longitudinal study of zuranolone showed that most patients who responded at day 15 received ≤2 treatment courses during ≤1 year of follow-up, suggesting that response to treatment is rapid and sustained.[43,44]

Conclusions

The therapeutic landscape for MDD is shifting to better address the delay in relief of symptoms experienced with current SOC ADTs. Patients with MDD with delayed response to treatment often experience worse clinical outcomes and lower HRQoL compared with those with rapid response. Some of the available treatments for patients with MDD demonstrate rapid improvement in depressive symptoms (eg, ECT, TMS, and esketamine) but are targeted for those with severe depression or TRD and require treatment at a specialized site with direct supervision by healthcare professionals, which may be particularly challenging for patients who are unable to find time to visit a treatment center or for patients in rural areas. Novel investigational therapeutic options offer the potential to achieve therapeutic efficacy within 1 week of treatment and demonstrate positive benefits, including a shorter time to remission, fewer residual symptoms, and greater HRQoL. Furthermore, several of the investigational agents are not associated with some of the treatment-limiting side effects commonly observed with SOC ADTs, such as sexual dysfunction, weight gain, and disturbed sleep. For some patients, these investigational therapies demonstrate favorable benefit-to-risk profiles relative to SOC ADTs. As more pharmacologic options with rapid and sustained effects enter clinical development and become available, it will be necessary to assess the accessibility of these treatment options and to adjust treatment expectations of patients and physicians. As such, a re-evaluation of the current "start low, go slow" clinical approach to pharmacotherapy for depression is critical, and will likely shift to one that targets individualized therapy that rapidly improves depressive symptoms without a significant side effect burden and need for chronic treatment.

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