Worldwide Clinical Trials

At a Glance: Rapidly-Acting Antidepressant Treatments

Revisiting the Clinical Imperative

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Timing is Key

The clinical imperative for fast-acting antidepressants stems from both the delayed onset of effect for traditional agents and the limited benefit often described. Conventional Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-norepinephrine reuptake inhibitors (SNRIs) take 4-8 weeks to demonstrate effect, while fast-acting antidepressant treatments can demonstrate full effect within days. This time difference can be life-changing for the patient, as they must manage symptoms while waiting for a traditional SSRI/SNRI to demonstrate a clinically meaningful effect. Rapid improvement is crucial, particularly for cases in which intrusive or organized thoughts of self-harm are present (e.g., suicidality). With the introduction of fast-acting antidepressants, patients with difficult-to-manage symptoms can experience relief at an accelerated pace. This allows them to regain more functionality in their day-to-day life and decrease the risk of harm or emergent medical disorders while waiting for the antidepressant medication to produce the anticipated, but nevertheless uncertain, therapeutic effect. Below, we've provided some representative modalities.

Representative Treatment Modalities

	Optimal Therapy	Traditional TCA/SSRI/SNRI	Enhancements Psychedelics	Devices TMS, VNS
Mechanism of Action	Biological data support target engagement	Serotonin/ Norepinephrine modulation	Complementary to / replacement of SSRIs	Electrophysiological
Indication	Antidepressive effect across diagnostic categories	Major Depression by DSM criteria	Major Depression with or without specifiers (e.g., MDD, TRD)	Various (e.g., MDD, TRD)
Differentiation	• Faster onset • Durability of effect • Remission > response • Absence of clinically important AEs • Addresses core and ancillary symptoms	• Established pedigree • Predictable onset • Established remission and response criteria	• Short time to efficacy (i.e., hours to days) • Enhanced response • Enhanced remission • Single dose applications	• Relative brisk onset • Short-term therapeutic intervention • Complementarity to established treatment modalities
Clinical Utility	• Effective across patient phenotypes • Useful in the presence of comorbidities • No relevant drug-drug interactions	• Amenable to widespread clinical use in diverse settings	• Brief, single-dose treatments • Potential for durability • Adjunctive to psychotherapy • Supervised settings	• Broader patient eligibility due to lack of concerns of comorbidity/drug-drug interactions
Design Considerations	• Diagnostic specificity • Baseline severity criterion • Timing of primary efficacy endpoint • Durability of effect • AEs are predictable, not clinically significant, and managed effectively in an outpatient setting	• Highly codified across major design elements	• Management of expectancy • Functional unblinding • Bespoke measures of early treatment effect • Enhanced surveillance within treatment sessions • Specific site selection criteria	• Clarification of dose-exposure response • Temporal/spatial applications

Long-Term Outcomes From Brief Treatment: SAINT-TMS & Esketamine

Developing clinical trial methodology to define the rapidity of antidepressant effect is fraught with uncertainty of operational definitions of response across various dimensions that can be present across depressive phenotypes. Nevertheless, various treatment paradigms have emerged that integrate both somatic (drug or device) and non-somatic (multiple forms of psychotherapy, especially cognitive behavioral therapy) interventions to maximize treatment response.

Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) transcranial magnetic stimulation (TMS), as an example, has quickly become a great tool in drastically improving depression remission rates within treatment-resistant depression (TRD). This treatment modality was approved in 2022 by the U.S. Food and Drug Administration for treating TRD.[1] SAINT is a 5-day, non-invasive, outpatient procedure in which patients feel relief within one week, and almost 80% of patients report going into remission following their treatment.[2] This program utilizes AI-guided simulation parameters to achieve maximal efficacy through personalized targeting based on individual brain mapping and accelerated TMS dosing. After initial treatment, it is possible to continue with maintenance treatments. However, maintenance treatment may be deemed unnecessary given evidence of durability that is clinically transformative.[2]

Intra-nasal esketamine has also become a new, fast-acting, and longer-lasting drug, potentially related to CNS neurogenesis demonstrated in animal models, which may enhance brain cell connectivity due to chronic stress. Esketamine increases the levels of glutamate in the brain, allowing for a greater impact on brain cells during treatment.[3] The postulated mechanism of action promoting molecular and structural neuroplasticity translates into rapidly enhancing dendritic spine growth and synaptogenesis, potentially explaining the durability effect commonly seen.[3] While this treatment modality is meant to be used in conjunction with a traditional SSRI/SNRI with decreased dosage frequencies, it is also compatible with conventional psychotherapeutic interventions, such as psychedelic-assisted therapy (e.g., psilocybin), which may have a comparable mechanism of action.

Medical Marijuana – Does it Help?

Medical marijuana, or cannabis and its constituents such as THC and CBD, is slowly becoming legalized across the United States. An important consideration is whether it may be another effective treatment for depression, especially given its widespread use by those with or without formal mood disturbances (i.e., depression). However, the FDA and other regulatory authorities have yet to approve cannabis for depression treatment, given the absence of consistent or compelling clinical trial results, including the use of inadequately controlled clinical investigations, which are “open label” and subject to the uncertainties that experimental design historically creates.

Furthermore, recent studies have suggested detriments of utilizing marijuana recreationally, such as worsened depression symptoms, increased suicidal ideation, and drug misuse.[4] Indeed, there may be a causal relationship in which heavy use can exacerbate mood disturbance, even though a quick reduction in depressive symptomology has been anecdotally noted. Additionally, if the correct genetic factors are present, marijuana use has been associated with an increased risk of psychosis or schizophrenia. Overall, the available literature does not provide a compelling justification for the use of marijuana in major affective disorders.

Cost-Efficiency & Access

Price point can often be a barrier to entry when it comes to seeking treatment and help for depression, and new fast-acting antidepressants are not immune to issues of economic accessibility. Indeed, access to novel pharmacotherapy is as much dictated by the economics of the transaction as it is by the clinical data supporting its use. As fast-acting antidepressant treatments are still new to the market, they may not be covered by insurance, making their high cost for treatment a stalling point for patients.

For example, SAINT therapy costs approximately 30K in USD or more for one week of treatment and is limited to a small number of treatment sites within the U.S. As time progresses, more of these newer antidepressants may be covered by commercial insurance plans, which significantly increases their access and affordability. In July 2025, Medicare and Medicaid made their first few

exemptions to cover SAINT in hospitals, allowing patients to benefit from increased accessibility and insurance coverage in the near future.

Commercial insurance carriers, in particular, will impose demands for demonstration of efficacy, including well-controlled trials that evaluate the rapid onset and durability. Efficacy and safety in specific subpopulations of depression, such as TRD or elderly patients, are optimally evaluated. In a treatment setting, the absence of complex special monitoring plans to ensure an acceptable risk-benefit ratio within clinical care is mandatory. The ability to inform economic evaluations, either based upon cost-effectiveness (characteristics of the E.U.) or budget impact analyses (characteristics of commercial plans in the U.S.), provides an opportunity to create a differentiated product profile. A representative evaluation of the "value" of intranasal esketamine is illustrative of the prism that is used to consider the utility of novel pharmacotherapy in depression.[5] Unfortunately, this may take longer than usual due to the high cost of treatment and the small number of locations offering this treatment.

Defining an "Optimal" Fast-Acting Antidepressant

Antidepressant treatments have evolved commensurate with innovative clinical trial methodology. Therefore, it is essential to consider what would be ideal for patients to enhance their overall clinical utility. Having a faster onset with the durability of the effect would help improve patient outcomes. For this "optimal" drug, utility across patient phenotypes would be laudable, and the absence of drug-drug interactions or restrictions based on the presence of comorbidities would be essential.

We can examine the various types of antidepressants currently on the market, as well as those in development, to see how each impacts patient health. Traditional SSRI/SNRIs have an extensive clinical database to inform their use, and novel, rapidly acting antidepressants could also be evaluated against this background of therapy. The introduction of rapidly acting antidepressants with sustained durability has the potential to transform the pharmacotherapy of depression and substantially address this critical unmet clinical need.

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