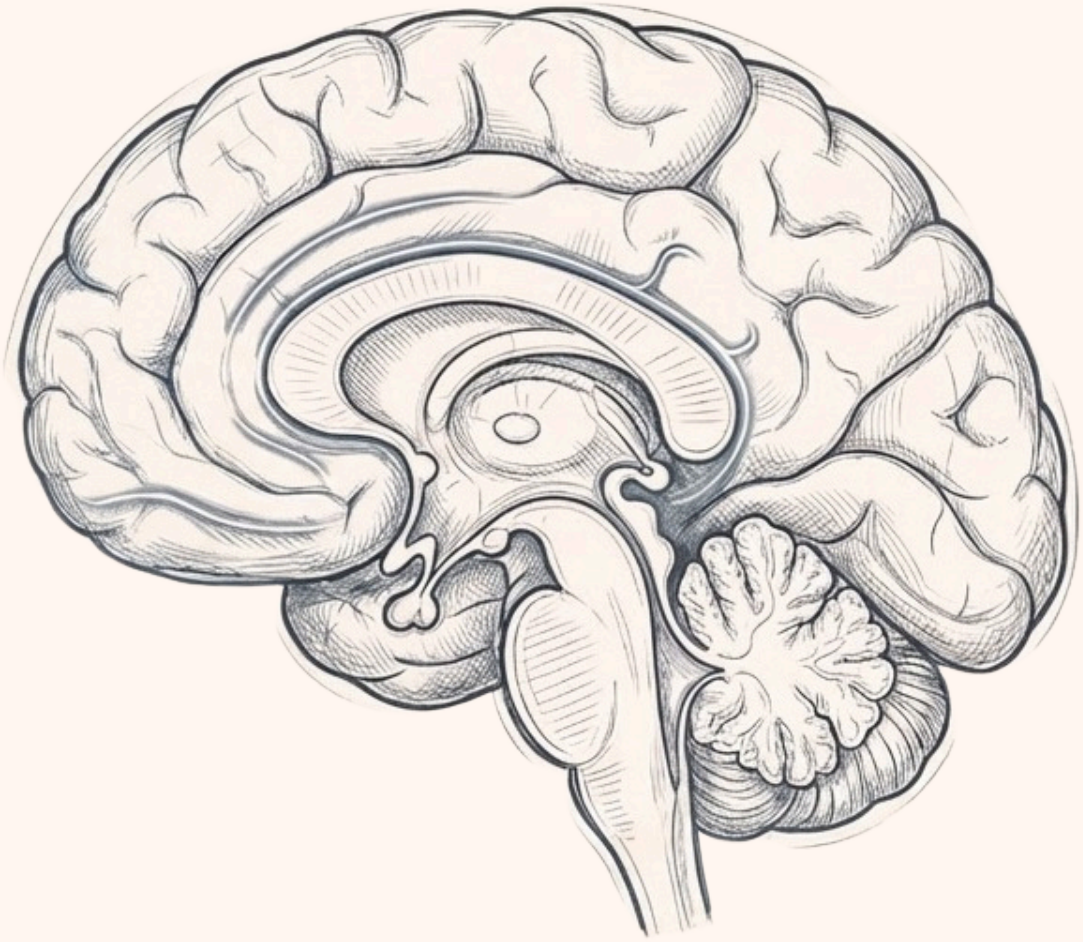
When Depression Treatment Stalls

A Biological Framework for Persistent Depression

A Guide for Medical Clinicians



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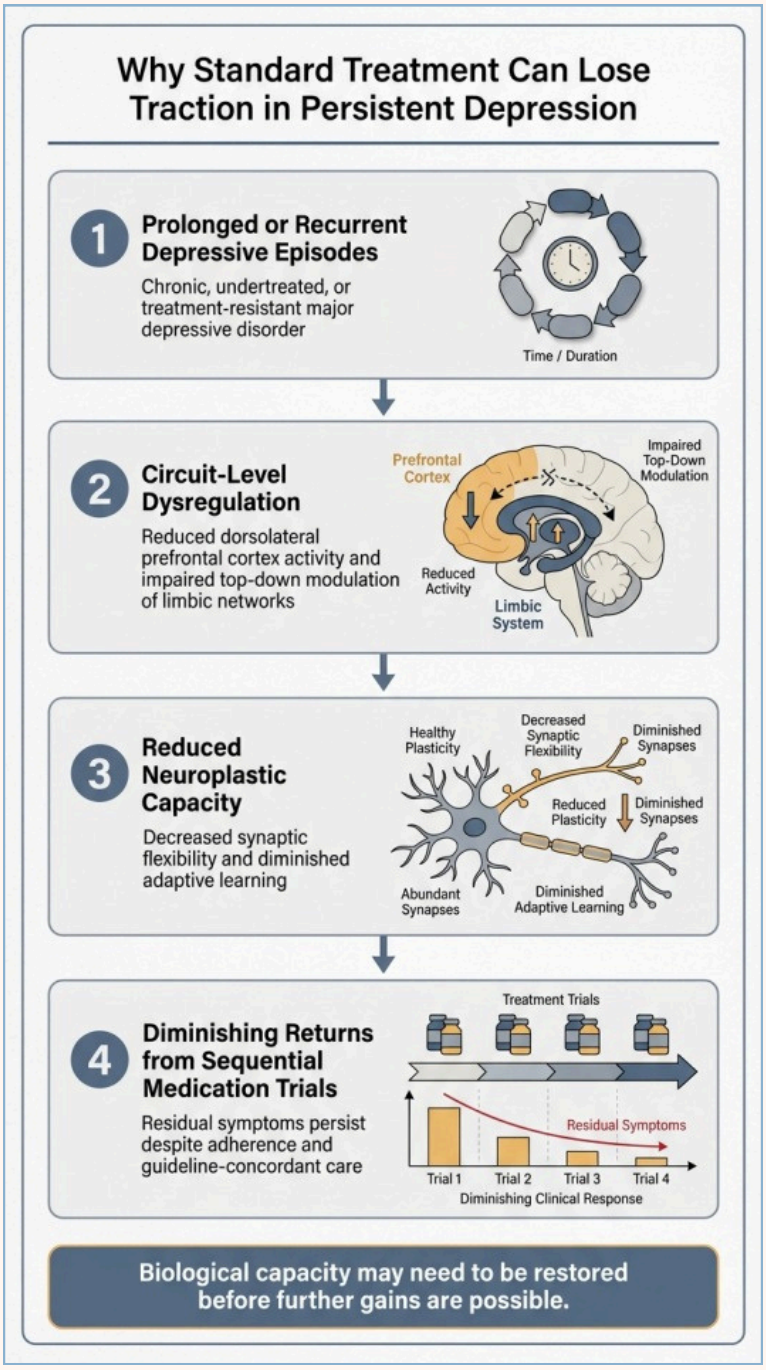
Why This Guide Exists

For the Clinician Managing Depression That Does Not Resolve

You are caring for a patient with depression who remains engaged in treatment. You have prescribed evidence-based medications. You have adjusted doses, switched classes, and considered augmentation options. The patient may also be participating in psychotherapy, sometimes for years. Despite appropriate, guideline-based care, improvement may remain partial, fragile, or absent.

This situation is common in real-world medical practice. Over time, it can lead clinicians to narrow treatment goals, accept residual symptoms as unavoidable, or continue cycling through familiar options with diminishing confidence. These decisions are usually made thoughtfully and with care for the patient's limits. Still, they often leave both clinician and patient feeling stuck in a holding pattern.



Why I Wrote This

I am Aazaz Haq, MD, an interventional psychiatrist who works primarily with patients suffering from severe and treatment-resistant depression. I wrote this guide to offer a clear, biologically grounded framework for understanding why depression can remain refractory despite appropriate pharmacologic and psychotherapeutic care, and how modern interventional approaches may help in selected cases.

In many of these patients, the limitation is not diagnostic uncertainty or inadequate treatment effort. It is the biological severity and chronicity of the illness itself. As depression persists, the brain's capacity to respond to conventional interventions may diminish. Recognizing this shift allows clinicians to move from repetition to strategy.

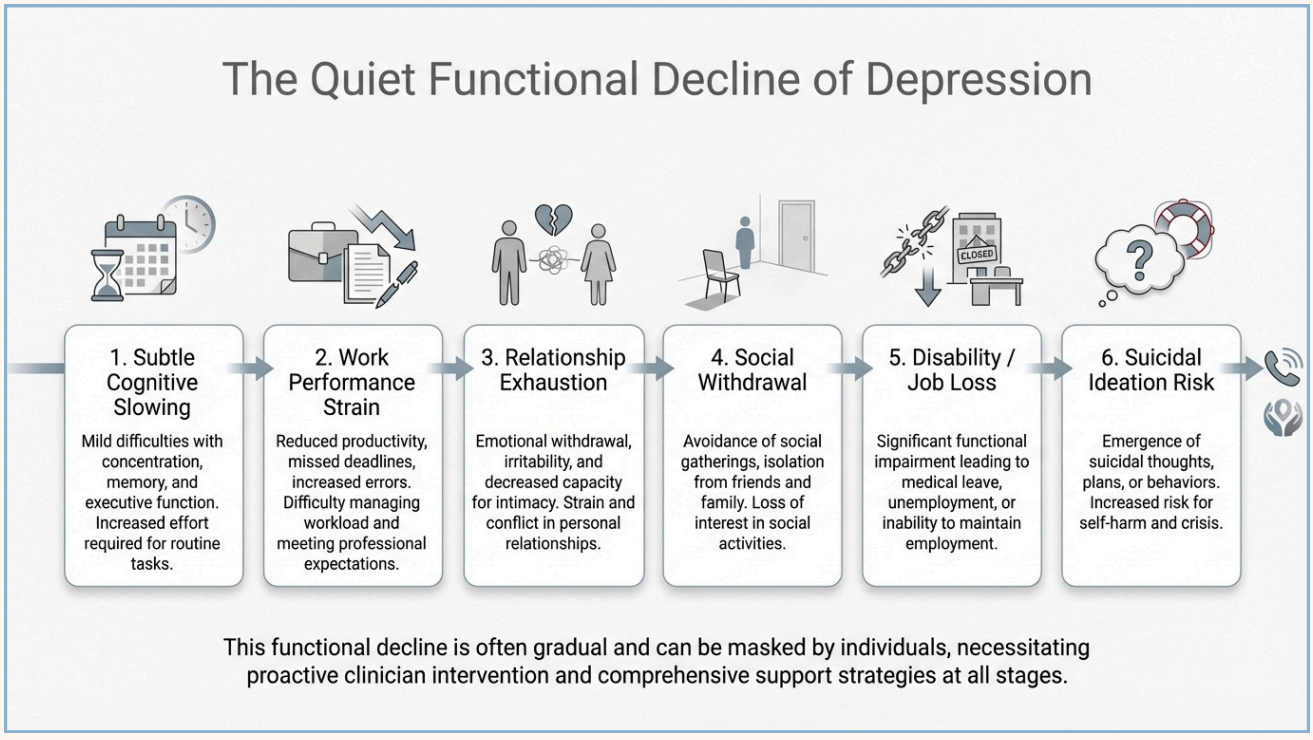
> ***Consider interventional psychiatry consultation when a patient with depression remains functionally impaired despite adequate medication trials, psychotherapy, adherence, and diagnostic reassessment.*** *Common signals include persistent cognitive slowing, declining work performance, social withdrawal, chronic hopelessness, recurrent passive death wishes, or repeated medication changes with limited durable benefit.*

Recognizing When Depression Becomes Treatment-Resistant

Major depressive disorder is highly prevalent and ranks among the leading causes of disability worldwide. In many patients, depression does not present as discrete episodes with clear recovery in between. Symptoms may persist or recur, with gradual decline in function that is difficult to appreciate during brief clinical encounters.

Early symptoms such as low mood, sleep disturbance, or fatigue are common and often responsive to initial treatment. Over time, more subtle markers may emerge. Concentration declines. Thinking becomes slower and less efficient. Decision-making becomes effortful. Patients remain adherent and engaged, yet their capacity to translate treatment into improvement narrows.

In primary care and psychiatric settings, changes in day-to-day function are often the clearest signal. Patients may continue to show up for work but function at a lower level, a pattern often described as presenteeism. Productivity falls, errors increase, and informal accommodations accumulate before formal leave or job loss occurs.[1, 2]



Clinical signal	What it may look like in practice
Cognitive Slowing	Longer time to complete routine tasks, reduced reading efficiency, difficulty organizing basic decisions.
Functional decline	Work performance declines despite attendance, informal accommodations increase, household tasks accumulate.
Emotional flattening	Less overt sadness, more numbness, indifference, or loss of emotional range.
Risk drift	Passive death wishes, chronic hopelessness, or statements such as “I cannot keep living this way.”

Social functioning tends to contract quietly. Patients decline invitations more frequently, communicate less, and gradually disengage from relationships. This withdrawal is not always driven by overt sadness. Many patients describe a shift from emotional distress to blunted indifference or emotional flatness.

From a risk perspective, persistent depression can evolve from episodic distress to chronic hopelessness. Passive thoughts such as “this is not sustainable” or “I cannot keep living this way” may become more frequent, even in the absence of acute suicidal intent. These signals are easily missed unless specifically assessed.

A common clinical definition of treatment-resistant depression is inadequate response to at least two antidepressant trials of adequate dose, duration, and adherence. STAR*D showed that remission rates generally fall as patients require additional medication steps, with remission rates of 36.8 percent, 3O.6 percent, 13.7 percent, and 13.O percent across the first through fourth acute treatment steps. At that point, persistent symptoms often reflect illness resistance rather than a lack of effort by the patient or clinician.[2, 3]

Hardware and Software: A Practical Way to Explain Treatment Resistance

One useful way to explain persistent depression is to think in terms of software and hardware. The metaphor is imperfect, but it helps distinguish treatments that work through psychological learning from treatments that act more directly on brain biology.

Psychotherapy often works through the software layer: insight, behavior, meaning, coping skills, and relationship patterns. It helps patients revise beliefs, process experiences, practice new behaviors, and build psychological skills over time. When the underlying system is responsive, these changes can take hold and compound. For many patients, this is sufficient.

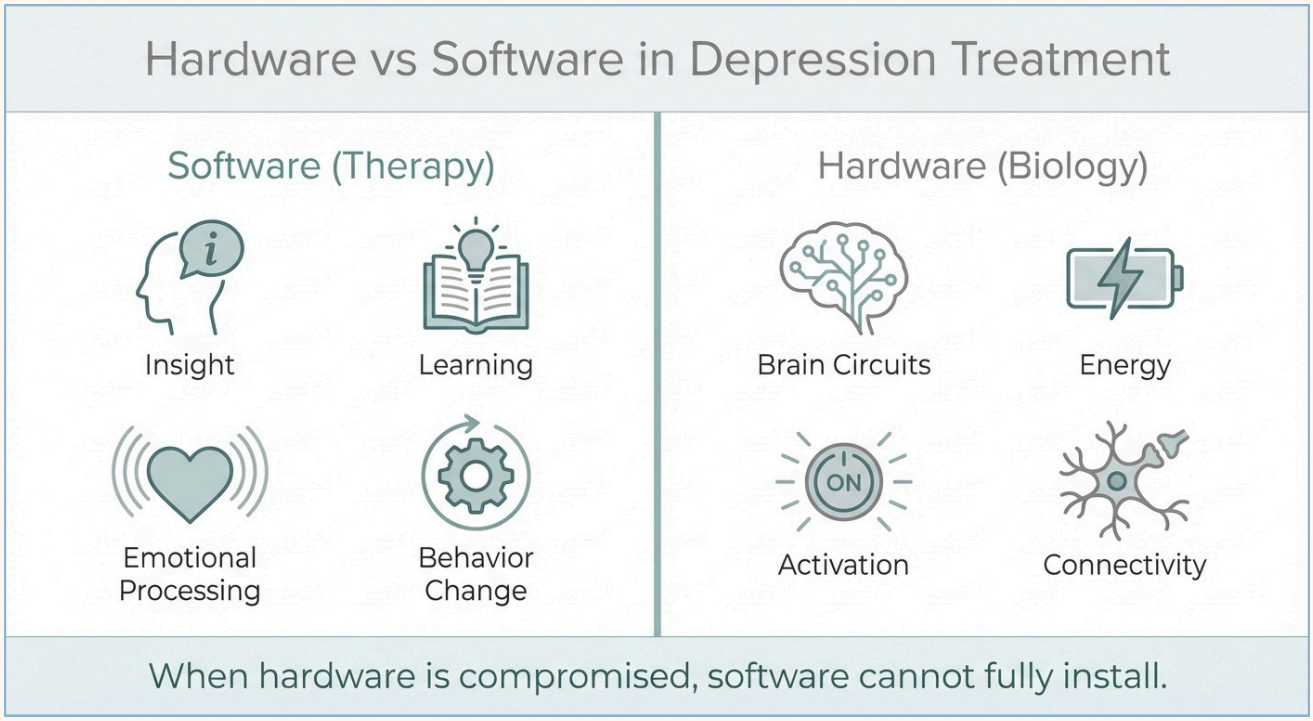
Medications and interventional treatments act more directly on brain biology, including neurotransmitters, brain circuit activity, and communication between brain regions. Clinicians already use brain-based biological tools routinely when prescribing antidepressants, mood stabilizers, antipsychotic augmentation, or electroconvulsive therapy. In many cases, these interventions meaningfully improve function and symptom burden.

In more severe or long-standing depression, the brain may be operating in a more constrained or stuck state. Brain circuits involved in mood regulation, motivation, reward processing, and executive function may become less flexible or less well coordinated. When this happens, conventional medication changes may not sufficiently shift the system.

Patients in this state often understand treatment recommendations and remain motivated to improve, but effort does not reliably lead to progress. Psychotherapy may feel cognitively correct yet emotionally inert. Medication changes may produce side effects without durable benefit. Clinicians and patients may find themselves repeating appropriate steps without seeing meaningful movement.

Interventional psychiatry expands the treatment options available when standard approaches have stalled. Treatments such as TMS and ketamine-based therapies can influence brain circuits and support plasticity, meaning the brain's ability to adapt and form new connections.[4, 9]

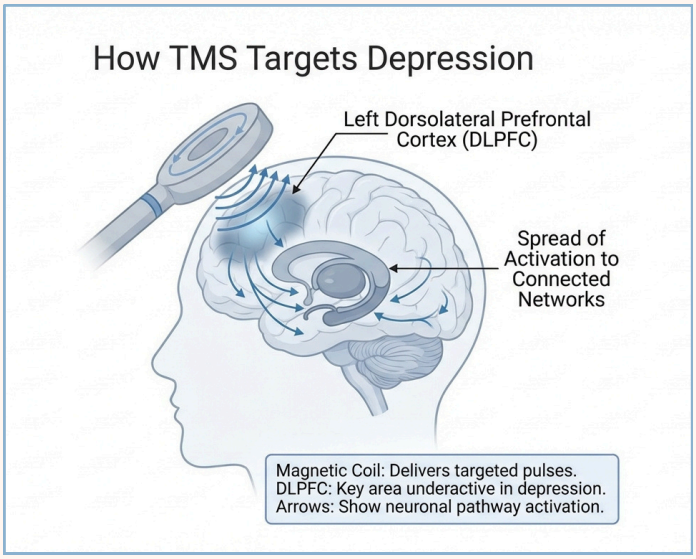
When brain function begins to improve, psychotherapy, medications, and the patient's own efforts may start to work again. Change can feel less effortful. Motivation may increase. Progress may become possible again, sometimes before mood fully normalizes.



Understanding Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation, or TMS, is supported by a large body of research linking depression with changes in prefrontal brain regions involved in mood regulation, cognitive control, and emotional processing. These findings help explain why targeted stimulation of prefrontal brain circuits became a rational treatment approach.[4, 10]

The dorsolateral prefrontal cortex plays an important role in executive functioning, working memory, planning, and regulation of emotionally charged information. When these systems are impaired, patients may report cognitive slowing, indecisiveness, reduced initiative, and difficulty sustaining effort, even when overt sadness is not the dominant complaint.



TMS uses a magnetic coil positioned over a measured scalp location corresponding to a targeted brain region. Rapidly changing magnetic fields pass through the skull and induce small electrical currents in the targeted area, influencing how those brain circuits function.[4]

When delivered repeatedly over a course of treatment, TMS may help shift brain activity and communication between brain regions in a clinically useful direction. The technology was first developed in the mid-1980s, and the first TMS device was cleared by the FDA for major depressive disorder in 2008.[4]

In real-world clinical practice studies, TMS has produced clinically meaningful response and remission rates in patients with persistent depression after antidepressant treatment. In one multisite observational study of 307 patients, clinician-rated response was 58.0 percent and remission was 37.1 percent. A later registry study of more than 5,000 patients reported response rates of 58 to 83 percent and remission rates of 28 to 62 percent across patient-rated and clinician-rated measures, with the important limitation that registry data are open-label and may be affected by selection bias.[5, 6]

TMS is targeted brain stimulation without anesthesia, sedation, or medication exposure throughout the body. Patients remain awake during treatment and generally can resume usual activities afterward. Many current protocols take under 20 minutes, although session length varies by protocol and device.

The most common adverse effects are transient headache and scalp discomfort, particularly early in treatment. Seizure is rare, and risk assessment should include seizure history, neurologic history, medications that lower seizure threshold, substance use, and relevant medical factors.[4]

Practical feature	What clinicians should know
Setting	Outpatient brain stimulation treatment.
Consciousness	No anesthesia or sedation.
Systemic exposure	No medication exposure throughout the body from the procedure itself.
Usual aftercare	Patients generally return to routine activities after treatment.
Common adverse effects	Transient headache or scalp discomfort.
Key safety screen	Seizure history, neurologic risk, medications, substances, and implanted or cranial metal or devices.

Understanding Esketamine and Ketamine

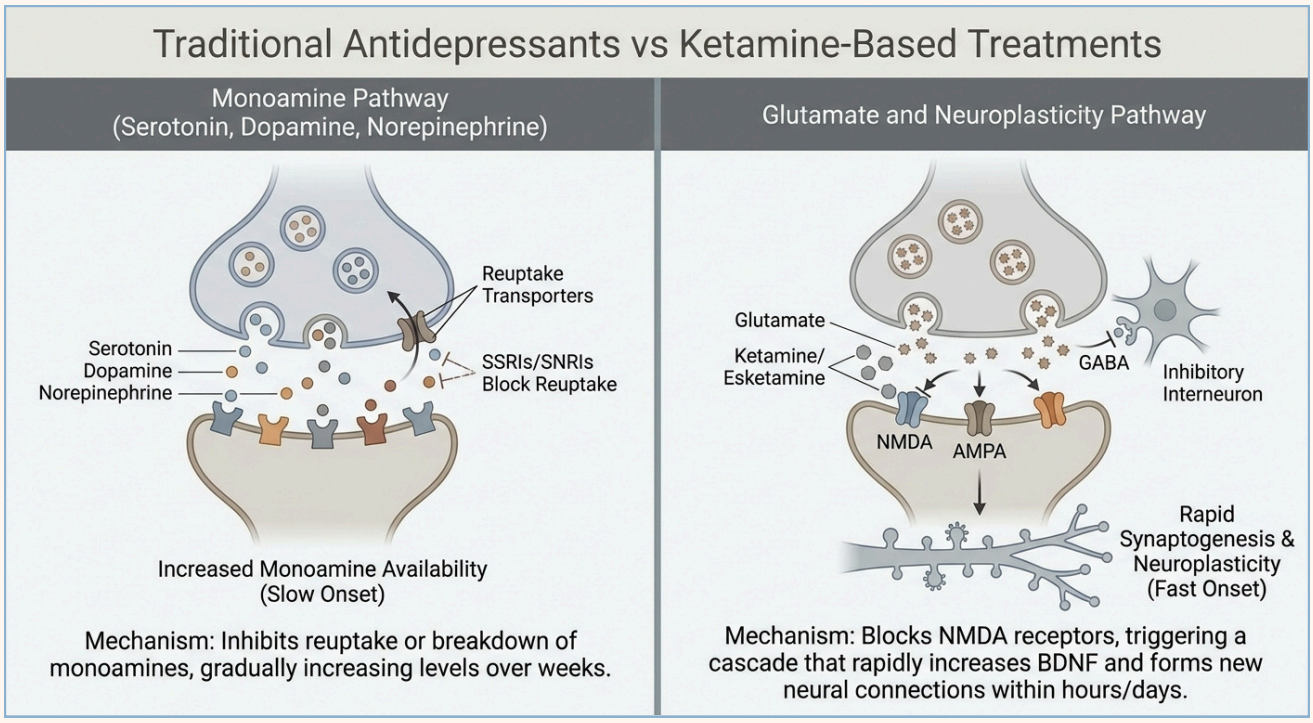
Esketamine and ketamine occupy a distinct place in depression treatment because they act through brain pathways that differ from those targeted by conventional antidepressants. For medical clinicians, this distinction helps explain why some patients who have not responded to multiple medication trials may still experience meaningful improvement with these interventions.

A Different Biological Pathway

Most conventional antidepressants exert their effects through monoamine pathways, primarily serotonin, norepinephrine, and dopamine. For many patients, changes in these pathways lead to symptom improvement. In others, particularly those with long-standing or treatment-resistant depression, repeated trials of traditional antidepressants produce diminishing returns despite adequate dosing, duration, and adherence.

Ketamine and esketamine act primarily through glutamate-related signaling, including NMDA receptor effects and related pathways involved in the brain's ability to strengthen and reorganize connections. This mechanism differs from traditional antidepressant strategies and helps explain the clinical interest in these treatments for treatment-resistant depression.[7, 9]

Clinically, ketamine-based treatments may create a temporary period of increased brain flexibility. During that window, patients may have greater capacity to disengage from entrenched depressive patterns and participate more effectively in ongoing treatment. The treatment works best when integrated with psychotherapy, medication management, and ongoing care, improving the brain's ability to respond to those treatments.



Regulatory Status and Clinical Context

Esketamine, marketed as Spravato, is an FDA-approved intranasal treatment for adults with treatment-resistant depression, as monotherapy or in conjunction with an oral antidepressant. It is also approved for depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior in conjunction with an oral antidepressant. It is administered under direct clinical supervision through a REMS program with post-dose monitoring.

Racemic ketamine was approved by the FDA in 1970 as an anesthetic. Its psychiatric use for depression is off-label, but supported by a substantial clinical research literature and expert consensus when delivered with appropriate patient selection, monitoring, and safeguards.[7, 9]

Treatment	Regulatory status in depression	Practical implications
Esketamine nasal spray	FDA-approved for adult TRD and for depressive symptoms in adult MDD with acute suicidal ideation or behavior, with indication-specific requirements.	Administered in certified clinical settings with REMS requirements and post-dose monitoring.
Racemic ketamine	FDA-approved as an anesthetic, used off-label in psychiatry.	Requires careful consent, screening, monitoring, documentation, and coordination with ongoing care.

Safety and Practical Administration

Esketamine treatment is delivered in certified clinical settings with monitoring after administration. The FDA label includes risks of sedation, dissociation, respiratory depression, blood pressure elevation, abuse and misuse, problems with attention, thinking, and reaction time, and impaired ability to drive or operate machinery until the next day after restful sleep.[7]

At the lower doses and structured schedules used in psychiatric care, ketamine treatment is administered in a medical model with screening, monitoring, and controlled access. Its abuse potential still requires careful patient selection, documentation, and follow-up, especially in patients with current or past substance use disorders.[7, 9]

Esketamine is typically initiated with a structured induction phase followed by reassessment and, when beneficial, maintenance treatment. Long-term follow-up data for esketamine have not identified a new safety signal through up to 4.5 years of periodic dosing among participants who continued in monitored treatment, although open-label extension data have important limitations and require careful interpretation.[8]

Benefits may diminish after discontinuation, which reinforces the importance of maintenance planning, ongoing psychiatric care, and realistic expectation-setting. Esketamine may cause fetal harm, breastfeeding is not recommended during treatment, and pregnancy planning and prevention should be discussed when relevant.[7]

Scope of Benefit

Ketamine-based treatments primarily target depressive illness. Research is ongoing in other psychiatric conditions, including PTSD, OCD, anxiety disorders, and substance use disorders, but these uses should be discussed as investigational or off-label unless supported by a specific indication, protocol, and patient-centered rationale.[9]

As with all interventional approaches, careful patient selection, expectation-setting, medical screening, and coordination with ongoing care are central to safe and effective use.

Who Is Most Likely to Benefit

TMS and ketamine-based treatments are best considered when depression remains clinically significant and functionally impairing despite appropriate first-line and second-line care. This often includes patients who remain adherent and engaged yet continue to experience biological symptoms that limit recovery.

In real-world medical practice, access and timing are shaped by clinical fit, coverage rules, logistics, and patient preference. Most insurance plans authorize TMS or esketamine only after documentation of treatment-resistant depression, commonly defined as failure of at least two adequate antidepressant trials. Requirements vary by payer and should be verified for each patient.[2, 7]

Factor	Clinical question
Adequate prior treatment	Have medication trials been adequate in dose, duration, adherence, and documentation?
Functional impairment	Is depression still limiting work, relationships, self-care, cognition, or safety?
Diagnostic reassessment	Have bipolar disorder, psychosis, substance use, medical contributors, and medication effects been considered?
Safety	Are there contraindications or risk factors that affect TMS, esketamine, or ketamine candidacy?
Logistics	Can the patient attend the treatment schedule and comply with monitoring and transportation requirements when applicable?
Ongoing care	Is there an established clinician or treatment team to continue care during and after interventional treatment?

Where TMS Fits Best

TMS is FDA-cleared for major depressive disorder in adults who have not achieved satisfactory improvement from antidepressant treatment. Other TMS indications and protocols are device-specific, and off-label use should be discussed separately from established MDD treatment.[4]

TMS may be especially relevant when a patient prefers a treatment without medication exposure throughout the body, has difficulty tolerating medication side effects, has persistent cognitive and motivational symptoms, or has depression that remains functionally impairing despite medication management.

Research continues across several neuropsychiatric conditions, but evidence strength varies by diagnosis, target, protocol, and device. For this guide, the clinically relevant focus is depression.[4]

Where Ketamine and Esketamine Fit Best

Ketamine-based treatments can be useful when depression is severe, persistent, and resistant to standard medication strategies, including when suicidal thinking is prominent. Esketamine is FDA-approved for treatment-resistant depression and for depressive symptoms associated with acute suicidal ideation or behavior under the conditions described in the prescribing information.[7]

Racemic ketamine is used off-label in psychiatry. When considered, it should be framed as a medically monitored intervention requiring careful selection, documentation, expectation-setting, and coordination with ongoing psychiatric care.[9]

Practical Takeaway

When you are caring for a patient with depression who remains engaged yet unable to gain traction, it is often reasonable to consider additional brain-based treatment support earlier than traditional sequencing habits might suggest. A more useful clinical question is whether the patient's current biology is likely to respond to more of the same treatment layer.

Clinical Collaboration & Referral

Supporting Referral When Standard Care Is Not Enough

For many clinicians, identifying when additional brain-based treatment may be appropriate is only part of the challenge. Finding a clinic that can evaluate patients carefully, communicate clearly, manage logistics reliably, and collaborate without disrupting ongoing care can be equally difficult.

Our aim is to serve as a dependable interventional resource for clinicians who are caring for patients with persistent or treatment-resistant depression. We focus on thorough psychiatric evaluation, thoughtful patient selection, evidence-based interventional treatment, and coordinated care, with attention to access, safety, and follow-through.

Our role is focused interventional consultation and treatment, with the referring clinician remaining the patient's ongoing clinical anchor.

How Collaboration Fits Into Ongoing Medical Care

By the time interventional options are considered, patients have usually already received substantial care. Medication trials have been conducted thoughtfully. Formulations are well developed. In many cases, psychotherapy is ongoing. At that stage, the brain's ability to respond may be the limiting factor even when diagnosis, adherence, and therapeutic engagement are strong.

In this context, collaboration with interventional psychiatry can be understood as a focused effort to improve the brain's ability to respond to ongoing care. The goal is to improve responsiveness so that existing treatments, whether medication-based, psychotherapy-based, or both, can regain clinical usefulness.

Collaborative principle	What it means in practice
The referring clinician remains central	Ongoing care, history, and continuity stay anchored with the established clinician.
Scope is defined	Interventional treatment targets depressive severity, reduced ability to respond, and functional impairment.
Communication is planned	Updates occur at clinically meaningful points rather than only when problems arise.

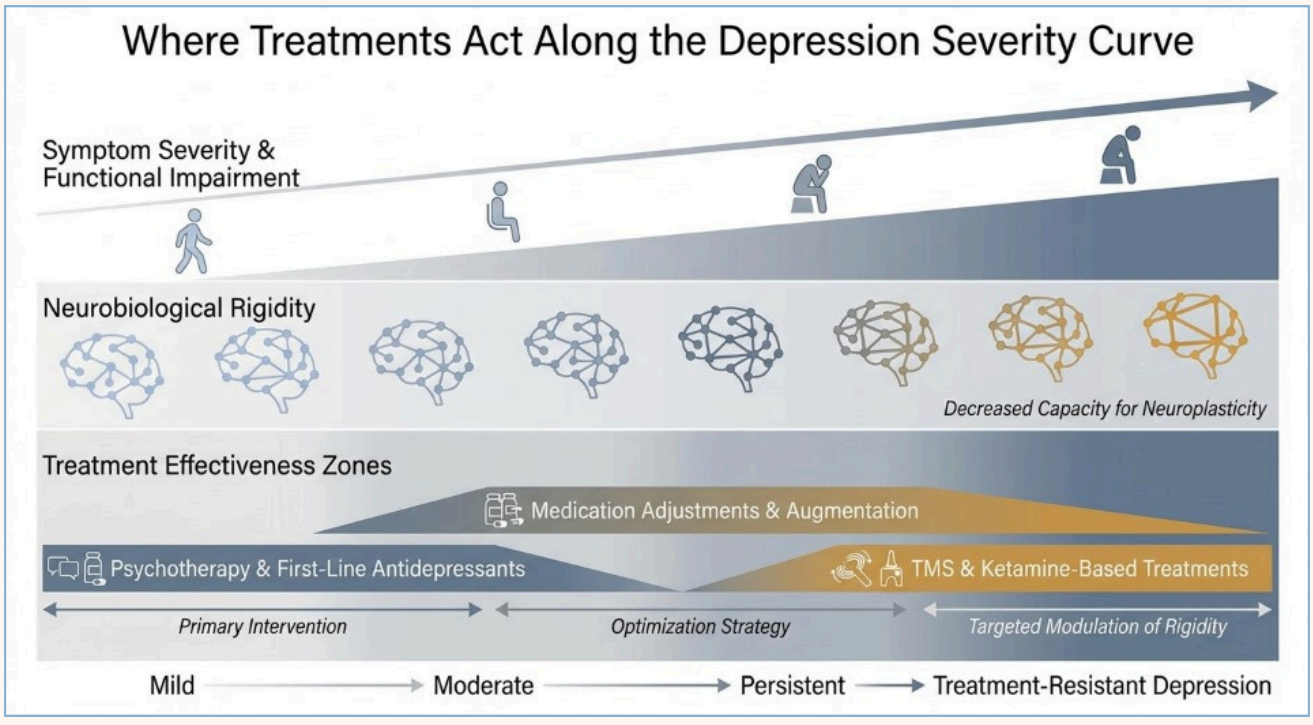
Collaborative principle	What it means in practice
Logistics are managed	Education, consent, insurance processes, scheduling, and monitoring are handled by the interventional team.
Step-back is expected	When the course of interventional treatment stabilizes, the patient remains connected to ongoing care.

This approach is not appropriate for every patient, and timing is important. In some cases, reassurance that current care remains appropriate is the most clinically responsible outcome. In others, temporary brain-based support can meaningfully alter the clinical trajectory.

What We Provide

Our clinic provides comprehensive psychiatric evaluation focused on treatment-resistant depression, with careful attention to diagnosis, prior treatment adequacy, safety, patient preference, and functional goals. When clinically appropriate, we offer evidence-based interventional treatments including TMS, esketamine, and ketamine.

We also provide clear patient education and expectation-setting regarding benefits, risks, limitations, logistics, and alternatives. When insurance authorization is applicable, our team manages the process and communicates requirements clearly. During treatment, we monitor response and safety, and we communicate with referring clinicians at key points in the course.



Service	Purpose
Comprehensive interventional psychiatry evaluation	Clarify diagnosis, treatment history, clinical fit, risk, and options.
TMS, esketamine, and ketamine evaluation	Match treatment options to clinical presentation, preferences, logistics, and safety profile.
Patient education and consent	Set realistic expectations about benefits, risks, time course, and follow-up.
Insurance and logistics support	Reduce administrative friction when authorization or structured scheduling is required.
Monitoring and outcome tracking	Assess response, tolerability, safety, and functional change over time.
Referring clinician communication	Provide focused updates without taking over ongoing care unless explicitly arranged.

Scope and Boundaries

Our involvement is focused, collaborative, and typically time-limited. Ongoing medical or psychotherapy care remains with the established clinician unless a different arrangement is explicitly discussed and clinically indicated. Treatment decisions are made conservatively and in alignment with the broader care plan.

A Low-Friction First Step

When it is unclear whether interventional treatment is appropriate, we offer an optional clinician-to-clinician consultation.

Clinician consult	Details
Length	10 to 15 minutes.
Focus	One specific patient.
Format	Case-based discussion.

Clinician consult	Details
Purpose	Clarify clinical fit, timing, safety considerations, and next steps.
Referral expectation	No requirement to refer afterward.

In many cases, the most helpful outcome is confirmation that continuing current care remains the best course.

How Referrals Work

If you and the patient decide to proceed, the patient may contact our clinic directly, or you may send a brief referral by email, secure fax, or your preferred clinical communication pathway. Our team manages patient education, consent, insurance processes when applicable, and treatment logistics. We provide updates as treatment progresses.

Our Commitment

We respect your clinical role and ongoing clinical relationship with the patient. We maintain clear boundaries around our role in care. We practice conservative clinical decision-making. We communicate at defined points in the treatment course.

Our goal is to reduce burden on referring clinicians while improving outcomes for patients whose depression has become biologically difficult to shift.

> *If you are unsure whether TMS, esketamine, or ketamine-based treatment is appropriate for a specific patient, a brief clinician-to-clinician consultation is the best first step. The goal is to clarify fit, timing, safety considerations, and next steps. There is no expectation that every consultation becomes a referral.*

Access the Provider Portal & Referral Forms

Click the link or scan the QR code to get started!

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Further Reading

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