It Takes a Village: Engaging Stakeholders in the Emerging Psychedelics Space

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Introduction

As we approach an inflection point in the use of psychedelic therapies globally, it is increasingly important to stay abreast of both the drivers of momentum and the barriers to acceptance in treatment-resistant depression (TRD). This report is based on a targeted literature review of the most recent information available as of April 2026 and focuses on TRD as a high-burden, high-cost endpoint of major depressive disorder (MDD) for which existing pharmacologic, psychotherapeutic, and neuromodulation strategies deliver only partial and often short-lived benefits for many patients. Using TRD as a case study, we highlight unmet needs and emerging psychedelic-assisted modalities across four key stakeholder groups (patients, regulators, providers, and payers/health technology assessment [HTA] bodies) and outline how real-world evidence (RWE) can support strategy, access, and implementation.

Throughout, we emphasize how a rigorous evidence strategy can help sponsors anticipate stakeholder expectations, de-risk development and launch, and ultimately improve outcomes for people living with TRD.

Background

MDD affects roughly one in five individuals over the lifespan, and an estimated 20-30% of these patients develop TRD, typically defined as failure to achieve a clinically meaningful response or remission after at least two adequate antidepressant trials.[1,2] In the United States (US), TRD affects millions of adults and is associated with markedly higher disability, healthcare utilization, and all-cause and suicide-specific mortality than treatment-responsive MDD, as well as substantial indirect costs from lost productivity and functional impairment.[1]

Despite a wide range of antidepressants and adjunctive options, approximately 30% of patients do not attain remission even after multiple medication switches and combinations.[3] Risk is increased by early-onset and severe illness, comorbid anxiety or trauma-related disorders, and socioeconomic disadvantage, and many patients follow a chronic, relapsing course with persistent functional limitations.[4] Standard TRD strategies include augmentation with atypical antipsychotics or lithium; combination pharmacotherapy; including evidence-based psychotherapies such as cognitive behavioral therapy; and neuromodulation techniques including electroconvulsive therapy (ECT), transcranial magnetic stimulation, and vagus nerve stimulation (VNS). These options can be effective for some individuals but are constrained by variable response rates, delayed onset, adverse effects (AEs), access barriers, and limited long-term durability, with diminishing incremental benefit at later treatment steps.[5]

Advances in understanding depression neurobiology, including abnormalities in large-scale brain networks, serotonergic and glutamatergic signaling, and inflammatory pathways, have helped explain the limited efficacy of purely monoaminergic approaches in TRD and motivated the development of novel interventions.[6] Glutamate-modulating agents such as ketamine and esketamine, and psychedelic-assisted therapies using compounds such as psilocybin or 3,4-methylenedioxymethamphetamine (MDMA), have shown rapid, large-magnitude reductions in depressive symptoms in early trials, with some patients maintaining benefit for weeks or months after a small number of dosing sessions.[6] These findings have driven substantial interest in the potential of psychedelic-assisted and other rapid-acting therapies to address the persistent symptomatic, functional, and quality-of-life (QoL) unmet needs in TRD. This white paper will cover the current unmet needs within TRD and the use of psychedelic therapy.

Against this backdrop, each stakeholder group brings distinct priorities and evidence expectations that should shape how psychedelic-assisted therapies for TRD are developed, evaluated, and brought into real-world practice **(Table 1)**.

Table 1. Summary of stakeholders involved in TRD, their key needs to address, and call-to-action to address the key needs.

Stakeholder	Key needs to address	Call to action
Patients	- Faster and more durable symptom relief, especially after multiple failed treatment steps. - Better functioning, HRQoL, and ability to work, maintain relationships, and manage daily life. - Reduced stigma, simpler access, and continuity of follow-up care across the treatment journey.	- Build development plans around patient-centered endpoints, including PROs, functioning, QoL, and acceptability. - Use evidence generation to document lived experience, access barriers, and unmet need in TRD. - Plan early RWE/HEOR programs that capture meaningful daily-life and productivity benefits.
Regulators	- Strong evidence on safety, abuse potential, blinding challenges, and supervised administration requirements for psychedelic-assisted therapies. - Clear data on durability, comparative effectiveness, and applicability beyond tightly selected trial populations. - Robust governance for monitoring, risk mitigation, and post-market evidence generation.	- Align early with evolving agency expectations and relevant precedents for supervised rapid-acting therapies. - Design studies that directly address durability, safety monitoring, and real-world-like populations. - Engage regulators early and often on endpoints, study design, and post-launch surveillance plans.
Providers	- Clear positioning of psychedelic-assisted therapy within TRD care pathways alongside ketamine, esketamine, ECT, and psychotherapy. - Practical solutions for staffing, training, credentialing, workflow, and supervision in real-world settings. - Confidence in safety protocols, ethics, consent, and management of vulnerable patients during altered states.	- Generate implementation-focused RWE on workflow, staffing, adherence, and safety in routine care. - Benchmark psychedelic-assisted therapy against current supervised and rapid-acting comparators. - Create evidence-based care-pathway and sequencing guidance to support provider adoption.

Stakeholder	Key needs to address	Call to action
Payers / HTA bodies	- Evidence that benefits are durable enough to justify high-touch delivery and monitoring costs. - Clear impact on utilization, hospitalizations, disability, absenteeism, and other major cost drivers in TRD. - Decision-grade economic models and RWE that reduce uncertainty around long-term value.	- Develop payer value stories grounded in economic burden, HRQoL, and unmet-need evidence. - Build flexible economic models that reflect realistic care pathways and can be updated with new RWE. - Prospectively plan claims/RWD studies to quantify utilization, costs, productivity, and durability after launch.

ECT: Electroconvulsive Therapy; HEOR: Health Economics and Outcomes Research; HRQoL: Health-Related Quality of Life; HTA: Health Technology Assessment; PRO: Patient-Reported Outcome; QoL: Quality of Life; RWD: Real-World Data; RWE: Real-World Evidence; TRD: Treatment-Resistant Depression

Patients: Prioritizing Burden, Barriers, and Lived Experience

TRD is associated with profound deficits in health-related quality of life (HRQoL) and functioning, and these deficits worsen with increasing treatment non-response. The Johnston et al. (2019) review of HRQoL studies found that patients with greater degrees of non-response had systematically lower scores on generic measures such as the SF-36/SF-12 and EQ-5D.[7] Prospective cohort studies show that while responders and remitters experience large improvements in mental-health domains and utilities, non-responders or partial responders show smaller gains and remain far below population norms, indicating substantial residual burden even after multiple treatment steps.[7,8] Large cross-sectional work in Europe and the UK similarly show that TRD is associated with markedly worse HRQoL and self-rated health than both the general population and non-TRD MDD, including lower physical and mental component scores and more pain, fatigue, and role limitations.

Beyond generic HRQoL indices, qualitative and mixed-methods evidence emphasizes the depth and breadth of the humanistic burden in TRD. The Talbot et al. (2022) thematic synthesis of treatment-resistant mental health conditions, largely driven by TRD, describes a “cyclic” pattern of crisis-driven help-seeking, short consultations, limited treatment options, and self-management of medication, with patients reporting feelings of being trapped, invalidated, and inadequately supported in primary care.[9] Many report persistent impairments in social relationships, identity, and sense of purpose, even when symptoms improve, and view antidepressants as offering limited or temporary benefit that does not address underlying psychological or social drivers of depression.[9]

Stigma is a recurrent theme across patient narratives. Public and self-stigma, including fear of being judged, labeled, or seen as a failure, delays help-seeking and contributes to secrecy, social withdrawal, and reluctance to disclose symptoms to clinicians.[9] Patients describe perceiving primary care as a setting where mental health is not prioritized and where they may not feel understood or supported, which can discourage continued engagement with treatment. Structural stigma, including coverage policies and bureaucratic hurdles, further separates people with severe or persistent symptoms from the clinicians and services they need.

Across conventional TRD treatments, onset of benefit is generally measured in weeks rather than days, and many patients relapse within 6-12 months, underscoring the appeal of rapid-acting interventions from a patient-centered perspective.[5,10]

Call to action for sponsors – anticipate the needs of patients

- Systematically characterize patient-level unmet needs in TRD, including HRQoL, functioning, stigma, and access barriers, using evidence generation syntheses, such as systematic literature reviews, to inform value propositions and trial endpoint selection.
- Design development programs that embed meaningful patient-reported outcomes (PROs) and lived-experience insights, ensuring that psychedelic-assisted therapies are evaluated not only on symptom change but on recovery, daily functioning, and acceptability.
- Consider early Health Economics and Outcomes Research (HEOR) and RWE planning focused on patient-relevant benefits (e.g., work participation, caregiving, social functioning) to support future payer and policy discussions.

While patients highlight the day-to-day realities of TRD and the limitations of current care, regulators focus on whether psychedelic-assisted interventions can meet evolving expectations for trial design, safety governance, and durability of effect.

Regulators: Guidance, Governance, and Evidence Expectations

Regulatory bodies play a central role in determining whether and how psychedelic-assisted therapies are integrated into TRD care. Esketamine (SPRAVATO®), a dissociative anesthetic often considered “psychedelic-adjacent,” illustrates a precedent for supervised, rapid-acting pharmacologic interventions as it is an FDA-approved intervention for adults with TRD and governed by a Risk Evaluation and Mitigation Strategy (REMS) that mandates supervised administration and post-dose monitoring.[11]

By contrast, psychedelics such as psilocybin remain investigational in TRD, and the FDA has issued draft guidance on psychedelic drugs emphasizing unique trial design considerations, including blinding challenges, abuse potential, acute psychological effects, and the need for robust safety monitoring and follow-up.[12] Breakthrough Therapy and other expedited designations signal regulatory pathways for such interventions and underscore the requirement for pivotal evidence that addresses durability, scalability, and risk mitigation acceptable to regulators and payers.

Beyond agency-level guidance, the single largest catalyst currently is arguably the April 18, 2026 Executive Order[13] signed by President Trump, aimed at loosening federal restrictions, allocating major funding, and fast-tracking clinical pathways for substances like psilocybin, MDMA, lysergic acid diethylamide, and ibogaine for mental health applications. The Executive Order allocates USD 50 million in federal funds to match state-level research efforts and represents the most significant federal shift in psychedelic policy since the Controlled Substances Act of 1971. Furthermore, there is growing bipartisan and veteran advocacy for psychedelic therapies, with veteran suicide rates being emphasized as a key motivator for accelerating success, especially with ibogaine and MDMA, due to their potential in treating post-traumatic stress disorder, depression, and addiction. Coupled with FDA momentum (granting Breakthrough Therapy status to psilocybin-assisted therapy for MDD and TRD), there is clear urgency being created by political will, regulatory momentum, funding, and public health pressure.[14]

Call to action for sponsors – anticipate the needs of regulators

- Align early with regulatory expectations by using systematic reviews and landscape assessments to synthesize evolving FDA/EMA guidance, precedents (e.g., esketamine REMS), and psychedelic-specific trial design considerations.
- Design programs that explicitly address regulatory concerns about durability, comparative effectiveness, safety in real-world-like populations, and governance of supervised administration.
- Engage regulators “early and often” to pressure-test study designs, endpoint strategies (including PROs), and safety-monitoring frameworks for psychedelic-assisted TRD therapies.

Regulatory requirements then flow downstream to the clinicians who must deliver these therapies safely and sustainably in routine practice.

Providers: Clinical Complexity, Workflow, and Real-World Effectiveness

Clinical burden

For providers, TRD is characterized by severe, persistent symptomatology, high suicidality, and multimorbidity, with many patients remaining in chronic episodes or recurrent partial remission despite intensive treatment. As the number of failed treatment steps increases, remission becomes less likely, and each subsequent line of therapy tends to yield smaller incremental benefits, reinforcing a trajectory of chronic symptoms and functional decline.[8]

Pharmacological management of TRD: current evidence and limitations

Conventional pharmacologic strategies, switching antidepressants, combining agents, and pharmacologic augmentation, can deliver clinically meaningful symptom reductions but only for a subset of patients and with modest effects on long-term outcomes.[5,6,10] Systematic reviews and network meta-analyses indicate that several augmenters and combinations outperform antidepressant monotherapy or placebo, yet acute response/remission rates rarely exceed 40–50%, and many patients remain symptomatic.[5,10] Tolerability and safety issues (e.g., metabolic complications, extrapyramidal symptoms, cognitive effects, falls, complex monitoring) further constrain their scalability, particularly in older or comorbid populations.[5,6,10]

Rapid-acting and psychedelic interventions: overview of emerging evidence and limitations

Rapid-acting glutamatergic agents and psychedelic therapies are frequently cited as promising solutions to these unmet needs.[6,10,15] Ketamine and esketamine are the most extensively studied rapid-acting pharmacological interventions. Across randomized controlled trials (RCTs) and meta-analyses in TRD, N-methyl-D-aspartate receptor modulators consistently produce large, rapid reductions in depressive symptoms and higher response and remission rates versus placebo.[6,10,15] However, durability remains a challenge; without structured maintenance, many patients relapse within weeks to months, and the need for supervised administration, monitoring, and management of dissociation and cardiovascular effects raises implementation questions in routine practice.[6,15]

Synthesize evidence on psychedelic-assisted therapies in TRD

Clinical evidence for psychedelic-assisted therapies is expanding, but TRD-specific randomized data remain relatively limited and largely early phase. The most informative TRD-specific RCT to date is the COMP360 international, phase 2b, double-blind, dose-ranging trial (N = 233), which evaluated a single administration of 25 mg, 10 mg, or 1 mg (active control group) synthetic, pharmaceutical-grade psilocybin, with structured psychological support.[16] At Week 3, the 25 mg arm showed significantly greater improvement in depression severity (Montgomery-Åsberg Depression Rating Scale) [MP1] [SG2] compared with 1 mg (least-squares mean difference = −6.6 points; $p < 0.001$), whereas 10 mg did not differ significantly from 1 mg (LSMD = −2.5; $p = 0.18$).[16] Durability was mixed: using the trial's protocol-defined sustained response through Week 12, sustained response occurred in ~20% (25 mg), ~5% (10 mg), and ~10% (1 mg), indicating that only a subset maintained benefit beyond the acute window.[16]

Within TRD specifically, the strongest published randomized evidence indicates a statistically significant reduction in depressive symptoms at 3 weeks after a single 25 mg dose of psilocybin compared with 1 mg active control.[16] In addition, COMPASS Pathways has publicly reported that two international phase 3 studies met their prespecified primary endpoints at Week 6 (topline results) in 2025-2026; however, peer-reviewed full datasets are needed to evaluate magnitude, durability, and safety in full.[17,18]

Because TRD decision-making increasingly values functional recovery and QoL, PROs remain policy-relevant even when trials are not statistically powered for them.[19] In an exploratory outcomes paper from the same COMP360 TRD trial by Goodwin et al., 25 mg psilocybin (vs 1 mg) was associated at Week 3 with broader improvements in patient-reported depression severity, anxiety, negative affect, and functioning/disability, with smaller effects at 10 mg.[19] By Week 12, effects were still clear, but differences between groups were weaker.[19] From an HTA and policy perspective, interpretation is limited by the lack of comparison to another active treatment and by the possibility of a lack of blinding – particularly for subjective outcomes like QoL and functioning. These limitations are particularly relevant for payer decision-making, where subjective endpoints carry lower evidentiary weight-absent proof from blinded or comparative designs.

Safety signals largely require careful attention in TRD populations. In the COMP360 phase 2b RCT, treatment-emergent AEs were common across groups, with headache, dizziness and nausea most prominent.[16] Additionally, self-injury and suicidal ideation or behaviour was observed across groups despite the exclusion of patients who were deemed to be at significant risk of suicide, highlighting the need for structured monitoring and follow-up.[16]

To position psychedelic models within TRD care pathways, it is important to consider established supervised, rapid-acting comparators, including procedural options such as ECT and supervised pharmacologic options such as esketamine/ketamine. An individual patient-level meta-analysis of randomized intravenous (IV) ketamine trials found robust antidepressant effects at ~24 hours and ~7 days, with larger effects in studies enrolling participants with greater prior treatment resistance.[20] In a large open-label, non-inferiority trial (N = 403) comparing IV ketamine (0.5 mg/kg over 40 minutes) with ECT, response at 3 weeks was 55.4% with ketamine versus 41.2% with ECT (difference: 14.2 percentage points; $p < 0.001$ for noninferiority), with differing tolerability trade-offs including QoL improvement, ECT-associated memory effects, and ketamine-associated dissociation.[21] A broader evidence synthesis further supports rapid effects across ketamine formulations while highlighting heterogeneity by formulation, dose, and timing window – relevant when positioning ketamine/esketamine as comparators for emerging psychedelic development programs.[22]

Beyond clinical efficacy, regulatory status and safety governance play a central role in determining how rapid-acting interventions are integrated into TRD care pathways. While esketamine (SPRAVATO®) is FDA-approved for adults with TRD with inadequate response to at least two oral antidepressants, and approved in 77 countries,[11] psychedelics such as psilocybin are classified in the US as investigational interventions, and the FDA has issued draft guidance describing unique trial design, conduct, and safety challenges.[12] While regulatory momentum exists (e.g., FDA Breakthrough Therapy Designation for psilocybin therapy in TRD[23]), this does not constitute approval and underscores that pivotal evidence must still address durability, safety governance, and scalable monitoring models acceptable to regulators and payers.[12]

Overall, the current evidence base supports rapid-acting, supervised interventions as an emerging category within TRD care. Phase 2 randomized evidence highlights meaningful short-term symptom reduction with high-dose psilocybin plus psychological support, with exploratory signals across functioning-related outcomes and QoL, while ketamine/ECT evidence provides a practical comparator framework for rapid onset and supervised delivery. From a policy standpoint, esketamine provides a regulated precedent for supervised psychoactive TRD treatment under a REMS framework, whereas psilocybin remains investigational under FDA guidance emphasizing trial design rigor and patient safety.

Call to action for sponsors – anticipate the needs of providers

- Use evidence generation projects to characterize clinical burden, multimorbidity, and provider-perceived unmet needs in TRD, and to benchmark psychedelic-assisted interventions against established options such as ketamine and ECT.
- Generate RWE that addresses real-world effectiveness, safety, and implementation (e.g., adherence to supervised protocols, resource use, staffing, and training) to support provider adoption and guideline inclusion.
- Develop clear, evidence-based care-pathway and sequencing narratives that help providers understand where psychedelic-assisted therapies may fit within TRD management.

The same issues that challenge providers, such as durability, safety, and implementation, are central to how payers and HTA bodies evaluate value of these interventions for reimbursement

Payers, HTA Bodies, and Market Access: Economic Value and Evidence Standards

Economic burden

A large body of observational and modeling work shows that TRD imposes substantially higher direct and indirect costs than both non-TRD depression and no depression, with costs rising steeply as treatment resistance deepens. In the Johnston et al. (2019) systematic review of economic studies, annual direct medical costs for TRD patients in US datasets typically ranged from approximately USD 12,000-19,000, consistently exceeding those for “managed” (non-TRD) depression and more than doubling the costs observed in non-depressed controls.[7] Across 10 studies, there was a clear gradient: each incremental level of treatment non-response was associated with higher total medical costs, driven by more frequent outpatient visits, emergency department use, and especially psychiatric and general hospitalizations.[7]

Hospitalization costs increased disproportionately compared with other categories and often accounted for one-quarter to over one-half of total direct costs among TRD-likely patients.

Indirect costs related to work loss and disability add substantially to this burden.[7] Claims-based and employer-focused analyses consistently report that TRD-likely employees have roughly twice as many days of absenteeism, higher disability rates, and significantly more total work-loss days than employees with non-TRD depression, translating into markedly higher indirect costs per person.[7] European and Canadian data similarly show higher rates of unemployment, disability benefit receipt, and reduced productivity in TRD compared with non-TRD MDD. Building on these cost-of-illness data, the Hannah et al. (2023) systematic review of economic evaluations highlights that newer interventions for TRD (e.g., neuromodulation, esketamine, psychotherapy and service-level models) are being assessed against a backdrop of high baseline cost and relapse risk, but long-term economic evidence remains limited and heterogeneous in methods, perspective, and utility data.[24] Taken together, current evidence supports TRD as a high-cost condition for health systems, employers, and society, with hospitalization and work disability as key cost drivers and substantial uncertainty about the long-term economic value of emerging treatments.

Moreover, at the population level, TRD is estimated to affect 30.9% of the 8.9 million adults with medication-treated MDD in the US, accounting for an estimated USD 43.8 billion of a USD 92.7 billion national burden of MDD.[25] European studies mirror this, with an Austrian cost-of-illness analysis estimating that indirect costs, such as productivity and disability-related losses, exceed direct medical costs, highlighting the importance of including societal cost components when characterizing TRD burden.[26] Economic evaluations in TRD highlight heterogeneity in TRD definitions and evaluation design, and are limited by gaps in high-quality long-term outcomes evidence.[24] A US model-based cost-effectiveness analysis suggests psilocybin-assisted therapy may offer economic value under certain assumptions such as overall intervention costs, but authors note the need to better understand longer-term effectiveness in maintaining remission and reducing relapse.[27]

Complementing these macro-level estimates, real-world claims analyses from a recent Komodo-based MDD/TRD cohort show that approximately 59% of TRD patients are covered by commercial health plans, 26.6% by Medicare, 13.6% by Medicaid, and only 0.4% by veterans affairs programs, underscoring that payer strategy will need to prioritize large commercial and Medicare plans while not neglecting Medicaid populations.

Accordingly, RWE capturing sustained clinical outcomes, healthcare utilization, and broader societal outcomes can validate model assumptions and support reimbursement decisions by agencies such as the Institute for Clinical and Economic Review (ICER), National Institute for Health and Care Excellence (NICE), and Canada's Drug Agency (CDA-AMC). Taken together, this RWE-HEOR nexus positions psychedelic-assisted therapies as potentially high-impact options for TRD, contingent on durable effectiveness, scalable delivery models, and safety governance frameworks that meet payer and regulatory expectations.

Call to action for stakeholders - payers and HTAs

- Develop payer value stories for psychedelic-assisted TRD therapies grounded in high-quality evidence syntheses of economic and HRQoL evidence, with transparent handling of heterogeneity and uncertainty.
- Build fit-for-purpose economic models that reflect realistic care pathways, long-term trajectories, and relevant perspectives (health system and societal), and that can be updated as new RWE becomes available.
- Plan prospective RWE programs designed to generate decision-grade data on utilization, costs, utilities, and productivity that meet the expectations of agencies such as ICER, NICE, and CDA-AMC.

As psychedelic-assisted therapies move from trials into real-world delivery, these evidence needs converge on a central question: can we reliably show, in routine practice, that efficacy translates into durable, economically meaningful benefit for people with TRD?

Final Call to Sponsors: Building an End-to-End Evidence Strategy for Psychedelic TRD Therapies

Psychedelic-assisted therapies are rapidly moving from promise to practice, entering a phase defined by approval, launch and delivery in routine care. In TRD, this transition exposes a central challenge: the condition remains difficult to define at scale in both clinical practice and real-world databases (e.g., claims/electronic health records). Patient populations show substantial heterogeneity in prior treatment exposure, treatment sequencing and clinical complexity – driven in part by variation in how 'adequate treatment' and 'clinically meaningful response' are interpreted. As a result, short-term efficacy (i.e., acute symptom reduction in controlled trials) – while essential – will not on its own be sufficient to address the questions that determine access and adoption, including durability, long-term safety and monitoring requirements, implementation feasibility, and comparative effectiveness and value in real-world settings.

Across patients, regulators, providers, and payers/HTA bodies, decision makers increasingly focus on outcomes that extend beyond symptom scales to functioning, QoL, and productivity, alongside the more traditional outcomes of durability of benefit, long-term safety, adherence and persistence, and performance outside of controlled trial settings. RWE provides a practical path forward to evaluate safety and cost-effectiveness of newly marketed TRD therapies. Claims-based and linked RWD should be considered as valuable data sources to operationalize TRD definitions, characterize patient journeys, quantify discontinuation and switching, and assess whether clinical gains translate into reduced healthcare utilization and meaningful economic value. The priority for sponsors is to embed HEOR and RWE early – building an integrated, end-to-end evidence strategy that complements clinical trials and supports regulatory confidence, reimbursement decisions, and scalable implementation. In considering low-cost options for longer-term post-market surveillance, sponsors may look to real-world data sources such as medical and pharmacy claims.

It is important to note that the absence of an ICD-10 code specific to TRD does not preclude interrogation of real-world data sources, and various workarounds have been used to identify TRD patients in these sources. One such workaround involves the use of a 'proxy' definition to create a cohort likely to have TRD.[28] This definition first identifies patients with MDD and further restricts to those who have been treated with alternative non-drug treatment options, such as ECT and VNS, which are commonly used in MDD cases that are not responsive to other treatments. Further investigations, such as demographic profile, payer information, patient treatment journeys, and medication adherence, can then be assessed in this cohort to obtain a more comprehensive picture. Other potential workarounds may involve assessing patients' patterns of switching/combining antidepressant medications, or the addition of an antipsychotic to the treatment regimen.

Conclusion

TRD is a prevalent, chronically disabling, and costly endpoint of MDD for which current pharmacologic, psychotherapeutic, and neuromodulation strategies deliver only partial, often short-lasting benefits for patients while leaving substantial residual symptoms, functional impairment, and loss of QoL. Rapid-acting, supervised interventions such as ketamine/esketamine and emerging psychedelic-assisted therapies offer a mechanistically novel way to address some of these unmet needs, with early TRD data showing rapid, clinically meaningful symptom reductions and encouraging signals for longer-term functional gains.

At the same time, durability of effect, comparative effectiveness versus established options, safety and governance in high-risk real-world populations, and equitable, economically sustainable delivery models remain unresolved questions that will determine whether these interventions can move from promising adjuncts to standard components of TRD care. Robust late-stage trials and coordinated HEOR/RWE programs linking clinical outcomes with healthcare utilization, costs, and productivity are essential to reduce uncertainty for regulators and payers. Comprehensive evidence generation will ensure that any future psychedelic-assisted therapies are implemented in ways that improve the lives of people with TRD and are accessible to those most affected by the disorder's clinical and socioeconomic burden.

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