Emerging Pharmacological Treatments for Major Depressive Disorder: A Narrative Review of Clinical Trials from 2023 to 2025

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Abstract
Major depressive disorder (MDD) remains a leading cause of global disability, affecting approximately 332 million individuals worldwide. Despite decades of monoaminergic antidepressant use, up to 60% of patients fail to achieve adequate remission with first-line therapies. This narrative review examines clinical trial evidence published between 2023 and 2025 for novel and emerging pharmacological treatments targeting non-monoaminergic pathways, including NMDA receptor antagonists (esketamine, dextromethorphan–bupropion, esmethadone), GABA-A receptor modulators (zuranolone), serotonergic psychedelics (psilocybin/COMP360), and kappa-opioid receptor antagonists (aticaprant). Efficacy outcomes are compared across drug classes using MADRS and HAM-D scales. The ESCAPE-TRD trial demonstrated esketamine's superiority over quetiapine in treatment-resistant depression (TRD), while psilocybin showed clinically meaningful sustained effects in phase 2 and phase 3 studies. Zuranolone received FDA approval for postpartum depression. Kappa-opioid antagonists showed promise in phase 2 but failed phase 3 endpoints. A tabular comparison of efficacy by drug class is provided. These findings illustrate a paradigm shift from serotonin-centric models toward rapid-acting, mechanism-driven interventions for depression.

Keywords: depression, antidepressants, esketamine, psilocybin, zuranolone, treatment-resistant, NMDA, clinical trials, pharmacotherapy

Introduction

Major depressive disorder (MDD) is among the most prevalent psychiatric conditions globally, with an estimated lifetime prevalence of 16% and approximately 332 million people currently affected. The World Health Organization reports that depression costs the global economy nearly $1 trillion annually in lost productivity, and suicide—strongly linked to depression—claimed an estimated 727,000 lives in 2021. In high-income countries, only about one-third of individuals with depression receive adequate mental health treatment.[1][2]

Traditional pharmacotherapy for MDD has relied heavily on selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs). While these agents represent effective first-line options, meta-analyses have shown only modest effect sizes compared with placebo (approximately 0.3), with overlap in

up to 88% of depression scores between drug and placebo groups. The landmark STAR*D study demonstrated that only about 67% of patients achieve remission after four sequential treatment steps, with remission rates declining at each level. Moreover, approximately 30% of patients with MDD meet criteria for treatment-resistant depression (TRD), defined as failure to respond to at least two adequate antidepressant trials. When more stringent definitions emphasizing symptomatic remission are applied, this estimate may rise to 55%.[3][4][5][6]

The limitations of monoaminergic antidepressants—including delayed onset of action (2–12 weeks), high rates of side effects such as sexual dysfunction and weight gain, and poor functional recovery—have spurred the development of novel agents targeting glutamatergic, GABAergic, opioidergic, and serotonergic psychedelic pathways. From 2009 through early 2025, the FDA approved 15 medications for depressive disorders, and 18 additional agents are in Phase 3 trials. The period 2023–2025 has been particularly transformative, with FDA approvals for dextromethorphan–bupropion (Auvelity, 2022), zuranolone (Zurzuvae, 2023), and gepirone (Exxua, 2023), alongside pivotal trial results for esketamine, psilocybin, and kappa-opioid antagonists.[4][7][8][3]

This narrative review aims to synthesize clinical trial evidence from 2023 to 2025 for emerging antidepressant agents, compare efficacy outcomes by drug class, and evaluate the implications of these data for the evolving treatment landscape of MDD and TRD.

Methods

This narrative review synthesized recent clinical trial literature published between January 2023 and December 2025. Electronic searches were conducted across PubMed, ClinicalTrials.gov, and major publisher databases (Frontiers, JAMA Network, Nature, The Lancet, NEJM). Search terms included "major depressive disorder," "treatment-resistant depression," "antidepressant clinical trial," "esketamine," "psilocybin," "zuranolone," "dextromethorphan–bupropion," "aticaprant," "esmethadone," and "novel antidepressant 2023–2025." Studies were selected based on clinical relevance, novelty of mechanism, regulatory significance, and availability of efficacy data from randomized controlled trials (RCTs) or pivotal registration studies. No systematic search or PRISMA methodology was employed. Outcomes of interest included change from baseline in Montgomery–Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAM-D) scores, response rates (≥50% reduction), remission rates, and safety profiles.

Results

NMDA Receptor Antagonists

Esketamine (Spravato)

The ESCAPE-TRD trial (NCT04338321), published in the New England Journal of Medicine in October 2023, was the first head-to-head RCT comparing esketamine nasal spray to quetiapine extended-release (XR), both combined with an ongoing

SSRI/SNRI, in patients with TRD. A total of 676 patients were randomized 1:1. At week 8, significantly more patients in the esketamine group achieved remission (MADRS ≤10) compared with quetiapine XR (27.1% vs. 17.6%; p = 0.003), and esketamine-treated patients were 1.54 times as likely to reach remission. At 32 weeks, esketamine maintained superiority: remission without relapse occurred in 21.7% vs. 14.1% of patients, respectively. A post hoc analysis demonstrated that esketamine was associated with significantly greater improvements in work productivity loss compared with quetiapine at both week 8 (−30.3 vs. −17.3 percentage points) and week 32 (−45.3 vs. −32.5 percentage points), translating to estimated weekly cost savings of $543 vs. $390. Sensitivity analyses confirmed the robustness of these results across different remission and relapse definitions.[9][10][11][12]

Dextromethorphan–Bupropion (Auvelity)

The phase 3 GEMINI trial (n = 327) demonstrated that dextromethorphan–bupropion (45 mg/105 mg twice daily) achieved remission in 39.5% of patients vs. 17.3% with placebo at week 6, with response rates of 54.0% vs. 34.0%. The MADRS mean change was −15.9 for the active group vs. −12.0 for placebo (LS mean difference ≈ −3.9). In the earlier phase 2 trial (n = 80), remission rates were even higher at 46.5% vs. 16.2% for bupropion alone. This agent was FDA-approved in August 2022 for MDD and represents the first novel oral antidepressant mechanism in over a decade, combining NMDA antagonism with sigma-1 receptor agonism and norepinephrine–dopamine reuptake inhibition.[3][7][13]

Esmethadone (REL-1017)

A phase 2a RCT evaluated esmethadone (25 and 50 mg daily for 7 days) as adjunctive therapy in patients with TRD. Both doses demonstrated significant improvements in MADRS scores with large effect sizes (0.9 and 1.0, respectively), sustained up to 7 days after treatment discontinuation. In a phase 1 study, esmethadone increased circulating BDNF levels up to 17-fold, supporting its neuroplasticity-promoting mechanism. Notably, esmethadone lacks the dissociative and psychotomimetic effects associated with esketamine and has minimal mu-opioid affinity, reducing abuse potential. Phase 3 trials are ongoing.[14][3]

GABA-A Receptor Modulators

Zuranolone (Zurzuvae)

Zuranolone was FDA-approved for postpartum depression (PPD) in August 2023 as a 14-day oral treatment course. The phase 3 CORAL study (NCT04476030), published in Neuropsychopharmacology in 2024, evaluated zuranolone 50 mg co-initiated with standard antidepressant therapy (ADT) vs. placebo + ADT in 425 adults with MDD. At the primary endpoint (Day 3), zuranolone + ADT showed significantly greater improvement in HAMD-17 total score (LS mean: −8.9 vs. −7.0; p = 0.0004), confirming rapid onset of action. A meta-analysis of seven RCTs (1,789 patients) confirmed that zuranolone reduced depressive symptoms (SMD = −0.37), increased response rates (OR = 2.06), and increased remission rates (OR = 2.04), with effects

sustained up to 45 days after cessation. The optimal therapeutic dose appeared to be 30 mg, with side effects (mainly somnolence and dizziness) increasing at doses exceeding 30 mg. While approved for PPD, the FDA declined approval for MDD as a monotherapy, citing insufficient evidence of sustained efficacy beyond the 14-day treatment window.[15][16][17][18]

Serotonergic Psychedelics

Psilocybin

The period 2023–2025 yielded landmark data for psilocybin in depression. In a phase 2 RCT published in JAMA (2023), Raison et al. randomized 104 adults with MDD to a single 25-mg psilocybin dose vs. niacin placebo, both administered with psychological support. Psilocybin demonstrated a mean MADRS difference of −12.3 points (95% CI: −17.5 to −7.2; $p < 0.001$) at day 43, with rapid onset by day 8 (−12.0; $p < 0.001$). Sustained response (≥50% MADRS reduction at all postdose visits) was achieved in 42% of the psilocybin group vs. 11% of niacin (OR = 5.6; $p = 0.002$). Functional disability scores also improved significantly. No serious treatment-emergent adverse events occurred, though the psilocybin group had higher rates of headache (66% vs. 24%) and nausea (48% vs. 6%).[19]

In June 2025, Compass Pathways reported positive results from COMP005, the first phase 3 trial of synthetic psilocybin (COMP360) for TRD. Among 258 participants randomized 2:1 to COMP360 25 mg or placebo, a single dose produced a statistically significant MADRS reduction of −3.6 points vs. placebo (95% CI: −5.7 to −1.5; $p < 0.001$) at week 6. An independent DSMB found no unexpected safety signals and no clinically meaningful imbalance in suicidal ideation. In February 2026, the second pivotal trial COMP006 also met its primary endpoint, with a MADRS difference of −3.8 points comparing 25 mg to a 1 mg control dose after two administrations three weeks apart. These represent the first-ever phase 3 efficacy data for a classic psychedelic compound.[20][21][22]

The 52-week follow-up study (COMP004), published in the Journal of Clinical Psychiatry in 2025, demonstrated that a single 25-mg dose of COMP360 maintained longer antidepressant effects compared with 1 mg and 10 mg doses, with average efficacy lasting approximately 12 weeks in the 25-mg group.[23]

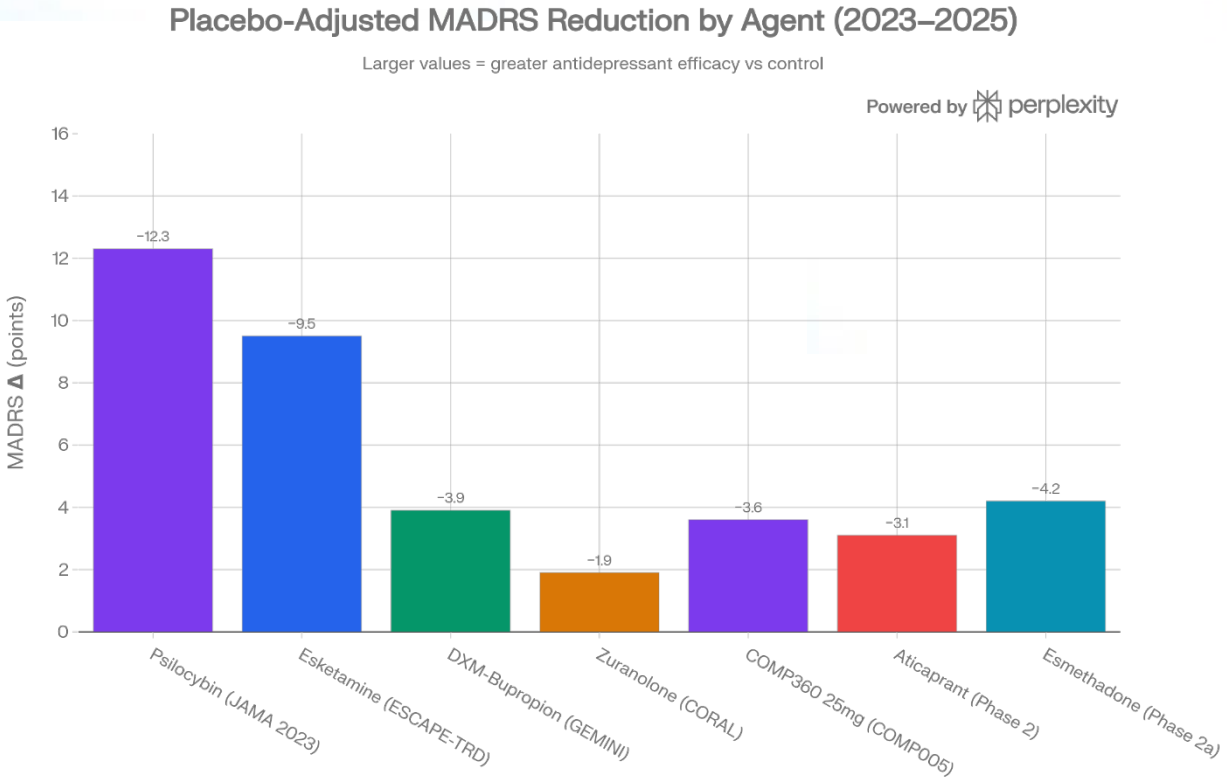
Kappa-Opioid Receptor Antagonists

Aticaprant

Aticaprant (JNJ-67953964), a selective kappa-opioid receptor antagonist developed by Johnson & Johnson, showed promising phase 2 results in MDD patients with inadequate SSRI/SNRI response. In a double-blind study (n = 184), adjunctive aticaprant 10 mg significantly reduced MADRS scores vs. placebo (LS mean difference: −3.1; $p = 0.002$; effect size 0.36), with larger benefits observed in patients with higher baseline anhedonia scores. However, in March 2025, J&J discontinued the phase 3 VENTURA program (VENTURA-1 and VENTURA-2 trials) after both studies failed to demonstrate sufficient efficacy in the target population of MDD

patients with moderate-to-severe anhedonia. Aticaprant was confirmed to be safe and well tolerated, but the primary MADRS endpoint at day 43 was not met. Similarly, Neumora Therapeutics' navacaprant, a competing KOR antagonist, also failed its phase 3 MDD trial in January 2025, raising fundamental questions about the viability of the kappa-opioid mechanism for MDD.[24][25][26]

Efficacy Comparison by Drug Class



The following tables summarize the efficacy outcomes from key clinical trials (2023–2025) organized by mechanistic drug class.

Table 1. NMDA Receptor Antagonists — Efficacy in Key Trials (2023–2025)

Agent	Trial	Phase	N	Comparator	Primary Endpoint	MADRS/HAMD Δ vs Control	Remission (%)	Response (%)	Onset
Esketamine NS	ESCAPE-TRD [9][10]	IIIb	676	Quetiapine XR + SSRI/SNRI	Remission at Wk 8	~−9.5 (MADRS MMRM)	27.1 vs 17.6 (p=0.003)	49.4 vs 32.8	Wk 2
DXM–Bupropion	GEMINI [7][13]	3	327	Placebo	MADRS Wk 6	−3.9	39.5 vs 17.3	54.0 vs 34.0	Wk 1
Esmethadone (REL-1017)	Phase 2a [3][14]	2a	~60	Placebo (TRD adjunct)	MADRS Day 7	ES 0.9–1.0	NR	NR	Day 4–7

Table 2. GABA-A Receptor Modulators — Efficacy in Key Trials (2023–2025)

Agent	Trial	Phase	N	Comparator	Primary Endpoint	HAMD-17/MADRS Δ vs Control	Remission (OR)	Response (OR)	Onset
Zuranolone 50 mg + ADT	CORAL [16]	3	425	Placebo + ADT	HAMD-17 Day 3	−1.9 (p=0.0004)	NR	NR	Day 3
Zuranolone (meta-analysis)	7 RCTs [17]	2/3	1,789	Placebo	Depression severity (SMD)	SMD = −0.37	OR 2.04	OR 2.06	Day 3

Table 3. Serotonergic Psychedelics — Efficacy in Key Trials (2023–2025)

Agent	Trial	Phase	N	Comparator	Primary Endpoint	MADRS Δ vs Control	Sustained Response (%)	Sustained Remission (%)	Onset
Psilocybin 25 mg	Raison et al. [19]	2	104	Niacin 100 mg	MADRS Day 43	−12.3 (p<0.001)	42 vs 11 (p=0.002)	25 vs 9.1 (p=0.05)	Day 8
COMP360 25 mg	COMP005 [20][21]	3	258	Placebo	MADRS Wk 6	−3.6 (p<0.001)	Pending full data	Pending full data	Wk 1–2
COMP360 25 mg (×2 doses)	COMP006 [22]	3	~300	1 mg control	MADRS Wk 6	−3.8 (p<0.05)	39% clinically meaningful	Pending	Wk 1–2

Table 4. Kappa-Opioid Receptor Antagonists — Efficacy in Key Trials (2023–2025)

Agent	Trial	Phase	N	Comparator	Primary Endpoint	MADRS Δ vs Control	Outcome	Notes
Aticaprant 10 mg	Phase 2 [24]	2	184	Placebo + SSRI/SNRI	MADRS Wk 6	−3.1 (p=0.002; ES 0.36)	Positive	Benefit greater in high-anhedonia subgroup
Aticaprant 10 mg	VENTURA-1 & -2 [25][26]	3	~600	Placebo + SSRI/SNRI	MADRS Day 43	Not significant	Failed	Program discontinued March 2025
Navacaprant 80 mg	Phase 3 [26]	3	~400	Placebo	MADRS	Not significant	Failed	Program halted January 2025

Table 5. Cross-Class Efficacy Comparison Summary (2023–2025)

Drug Class	Representative Agent	Best MADRS Δ vs Control	Fastest Onset	FDA Status (2025)	Key Advantage	Key Limitation
NMDA antagonists	Esketamine NS	−9.5 (ESCAPE-TRD)	Hours–days	Approved (TRD, 2019)	Head-to-head superiority vs quetiapine	In-clinic monitoring, dissociation, abuse potential
NMDA + sigma-1	DXM–Bupropion	−3.9 (GEMINI)	Week 1	Approved (MDD, 2022)	First novel oral mechanism; oral, outpatient	Modest effect size vs placebo
GABA-A modulators	Zuranolone	−1.9 (CORAL); SMD −0.37 (meta)	Day 3	Approved (PPD, 2023); MDD under review	Rapid onset, 14-day oral course	Efficacy gap in general MDD; short course
Psychedelics (5-HT2A)	Psilocybin 25 mg	−12.3 (Raison/JAMA)	Day 8	Not approved; Breakthrough (Phase 3)	Largest effect size; sustained from single dose	Functional unblinding; supervised setting required
Kappa-opioid antagonists	Aticaprant	−3.1 (Phase 2)	Week 2–4	Discontinued for MDD (2025)	Targeted anhedonia	Phase 3 failure; mechanism unvalidated for MDD

Discussion

The 2023–2025 period has witnessed a decisive shift in the pharmacological treatment of depression away from the monoamine hypothesis toward mechanism-driven, circuit-level interventions. The data reviewed here carry several important implications for clinical practice and future research.

The ESCAPE-TRD trial stands as a watershed moment, providing the first randomized evidence that esketamine nasal spray is superior to an active comparator (quetiapine XR) rather than merely placebo. The clinical significance of this finding is underscored by the fact that quetiapine augmentation has been a mainstay of TRD treatment in real-world practice. With remission rates of 27.1% vs. 17.6% and sustained relapse-free remission of 21.7% vs. 14.1%, esketamine offers a meaningful clinical advantage, though the absolute difference remains modest. Sensitivity analyses and secondary outcomes, including work productivity improvements, have strengthened the evidence base.[9][10][11][12]

Psilocybin represents perhaps the most striking mechanistic departure from conventional antidepressants. The Raison et al. (2023) trial is notable for its large

placebo-adjusted MADRS difference of 12.3 points—exceeding the upper limit of what is considered clinically substantial in the depression trial literature. The sustained response rate of 42% from a single administration is remarkable given that conventional antidepressants require weeks to months of daily dosing. The COMP005 and COMP006 phase 3 results, while reporting more modest MADRS differences (−3.6 and −3.8, respectively), must be interpreted in the context of larger sample sizes, placebo/low-dose control designs, and the stringent regulatory environment of pivotal trials [20–22]. Importantly, COMP005 and COMP006 represent the first phase 3 data for any classic psychedelic, marking a regulatory milestone [20–22].[19]

Zuranolone's rapid action (onset at Day 3) fills a critical temporal gap during which patients initiating standard ADT remain symptomatic. Its approval for PPD validates the GABA-A modulation hypothesis, though its role in general MDD remains uncertain after the MOUNTAIN study failed its primary endpoint and the FDA declined the MDD indication. The CORAL study, by demonstrating benefit when co-initiated with ADT, suggests zuranolone may serve best as a "bridge" therapy rather than a standalone agent.[15][16][17][18]

The failure of kappa-opioid antagonists in phase 3 represents a significant setback. Despite robust preclinical rationale and encouraging phase 2 data for aticaprant—particularly in patients with high anhedonia scores—both the VENTURA program and navacaprant's phase 3 trial failed to meet primary endpoints [24–26]. These results raise important questions about whether anhedonia-specific targeting can be adequately captured by broad instruments such as the MADRS, or whether subpopulation enrichment strategies in these trials were insufficient. The kappa-opioid mechanism may yet prove viable in other indications or with refined patient selection.[26]

Several limitations apply to this review. As a narrative synthesis rather than a systematic review, publication bias and selective reporting may influence the evidence base. Head-to-head comparisons across drug classes are largely absent; the efficacy values presented in the tables derive from different trial populations, study designs, and comparator conditions, limiting direct cross-class comparison. Additionally, long-term safety and durability data remain limited for most agents, particularly psilocybin and esmethadone. Future research should prioritize comparative effectiveness trials, biomarker-guided patient selection, health economic analyses, and longer-term follow-up studies to fully characterize the real-world utility of these emerging therapies.

Conclusion

The treatment landscape for major depressive disorder is undergoing a fundamental transformation. The 2023–2025 clinical trial evidence demonstrates that agents acting on glutamatergic (esketamine, dextromethorphan–bupropion), GABAergic (zuranolone), and serotonergic psychedelic (psilocybin) pathways can deliver rapid, clinically meaningful antidepressant effects that address critical limitations of traditional monoaminergic therapies. Esketamine has established head-to-head superiority over quetiapine in TRD, psilocybin has achieved phase 3 success with

sustained benefits from a single administration, and zuranolone has introduced the first oral rapid-acting agent for postpartum depression. Conversely, the phase 3 failure of kappa-opioid antagonists underscores the complexity of translating mechanistic promise into clinical efficacy. As these agents advance through regulatory pathways and into clinical practice, the field stands at the threshold of a new era in depression pharmacotherapy—one defined not by monoamine modulation alone, but by a diverse armamentarium of mechanism-specific, rapid-acting interventions that may finally close the remission gap for the millions of patients who remain inadequately treated.

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