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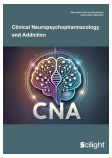

Review

Novel Perspectives for Glutamatergic Strategies, Psychedelics and Antipsychotic Augmentation in Treatment Resistant Depression: A Narrative Review

Clara Cavallotto [1,*], Stefania Chiappini [2], Andrea Miuli [3], Giacomo d'Andrea [1,3], Alessio Mosca [1], Carlotta Marrangone [1], Rita Allegretti [1], Serena Panichella [1], Antonio D'Attilio [1], Giovanna Mammarella [1], Luca Persico [1], Alessia Santeusanio [1], Gianfranco Tamagnini [3], Mauro Pettorruso [1,3] and Giovanni Martinotti [1,3]

[1] Department of Neurosciences, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti—Pescara, 66100 Chieti, Italy
[2] School of Medicine, UniCamillus International Medical Sciences University, Via di S. Alessandro 8, 00131 Rome, Italy
[3] Department of Mental Health, ASL 02 Lanciano-Vasto-Chieti, 66100 Chieti, Italy
* Correspondence: clara.cavallotto@laconchiglia.srl

How To Cite: Cavallotto, C.; Chiappini, S.; Miuli, A.; et al. Novel Perspectives for Glutamatergic Strategies, Psychedelics and Antipsychotic Augmentation in Treatment Resistant Depression: A Narrative Review. *Clinical Neuropsychopharmacology and Addiction* **2025**, *1*(1), 6. https://doi.org/10.53941/cna.2025.100006

Received: 14 August 2025
Revised: 28 August 2025
Accepted: 23 September 2025
Published: 25 September 2025

Abstract: Introduction: Treatment-Resistant Depression (TRD) affects approximately 30–50% of patients with Major Depressive Disorder (MDD) who fail to respond to at least two adequate antidepressant trials. This condition presents substantial clinical and functional challenges, and no universally accepted treatment algorithm currently exists. Emerging therapeutic strategies, particularly glutamatergic modulators and psychedelics, have shown promising results in managing TRD. Methods: We conducted a narrative review using PubMed and Scopus with the query "(treatment resistant depression OR TRD) AND (glutamatergic OR glutamate OR psychedelic OR psilocybin OR antipsychotic augmentation) NOT (review OR animal OR mouse)." After applying inclusion/exclusion criteria, 60 articles were selected. Results: The most frequently studied treatments (43 studies) are glutamatergic agents, particularly intravenous ketamine and intranasal esketamine, which have consistently demonstrated rapid and clinically meaningful reductions in depressive symptoms. Augmentation with atypical antipsychotics also showed effectiveness for partial responders. Psychedelic-assisted therapies yielded sustained antidepressant benefits and modulated biomarkers such as BDNF and inflammatory markers. Discussion and Conclusion: The findings support a potential paradigm shift away from traditional monoaminergic-based treatments toward more personalized, mechanism-driven strategies for managing TRD. Ketamine and esketamine offer rapid-onset relief suitable for acute high-risk cases, while augmentation strategies remain valuable for partial responders. Psychedelic interventions, although still experimental, hold promise as adjunctive options. Furthermore, biomarkers and early response predictors may help guide individualized treatment decisions.

Keywords: treatment resistant depression; ketamine; esketamine; psychedelic; psilocybin; antipsychotic augmentation

1. Introduction

1.1. The Landscape of Treatment Resistant Depression (TRD)

Major Depressive Disorder (MDD) represents one of the most prevalent and debilitating psychiatric conditions worldwide, currently affecting over 300 million individuals across diverse populations [1]. Its impact extends beyond personal suffering, contributing substantially to the global burden of disease and disability. A growing body of research indicates that MDD is not a singular or uniform disorder but rather a complex and heterogeneous condition with multiple underlying pathophysiological mechanisms [2]. Despite the availability of numerous pharmacological and psychotherapeutic interventions, clinical outcomes remain suboptimal for a significant subset of patients. Approximately 30–50% of individuals diagnosed with MDD fail to achieve adequate relief from symptoms following initial treatment efforts [3]. This lack of response often leads to prolonged suffering and functional impairment, with a considerable proportion eventually meeting criteria for Treatment-Resistant Depression (TRD). TRD is typically defined as the failure to attain a clinically meaningful improvement in depressive symptoms despite undergoing at least two antidepressant treatment trials, each of which must be considered adequate in both duration (commonly a minimum of 4–6 weeks) and dosage [4].

Currently, a variety of therapeutic approaches are utilized in routine clinical practice. These strategies include augmentation therapies involving agents such as lithium and atypical antipsychotics, which are often employed to enhance the efficacy of existing antidepressant regimens [5]. Additionally, dose optimization through careful titration is commonly used to maximize therapeutic response [5]. Other widely adopted interventions include switching strategies, both within and between pharmacological classes of antidepressants, as well as combination therapies that involve the concurrent use of multiple antidepressants with complementary mechanisms of action [5].

Nevertheless, at present there is no universally accepted or standardized set of therapeutic guidelines for the management of TRD. This lack of consensus poses significant challenges for clinicians, as TRD represents a particularly complex and heterogeneous clinical entity.

1.2. Emerging Therapeutic Approaches for the Management of TRD

A growing body of evidence has identified the dysregulation of glutamatergic neurotransmission as a particularly relevant factor in the pathogenesis of TRD [6]. In this context, recent years have seen increasing interest in ketamine and its S-enantiomer, esketamine, which specifically target this glutamatergic dysfunction. These compounds act as noncompetitive antagonists of the N-methyl-D-aspartate (NMDA) receptor and have shown significant antidepressant efficacy in patients with both unipolar and bipolar depression [7–12] These findings mark a significant advancement in the treatment landscape of mood disorders, particularly for patients who do not respond to conventional therapies.

In 2019, this therapeutic innovation gained regulatory recognition when both the FDA and EMA approved the clinical use of esketamine nasal spray (ESK-NS) for the treatment of TRD in adult populations [13,14]. Since then, a growing body of real-world and clinical research has further validated its efficacy, safety, and tolerability. Notably, a multicenter naturalistic study involving patients with both unipolar and bipolar TRD confirmed the antidepressant effectiveness of ESK-NS, reinforcing its clinical utility in complex, treatment-refractory cases [11,15]. Similar therapeutic benefits have also been observed in substance use disorder and elderly populations suffering from TRD [16,17].

Parallel to these developments, psychedelic compounds have garnered increasing attention as potential therapeutic agents in the treatment of various psychiatric disorders, including mood and anxiety-related conditions. The mechanisms of action underlying these effects appear to be multifaceted. Psychedelics are believed to produce antidepressant outcomes through both direct serotonergic receptor agonism, particularly at the 5-HT2A receptor, and indirect pathways, which include alterations in neuroplasticity, modulation of inflammatory and neuroendocrine markers (e.g., cortisol), and shifts in functional brain activity. These neurobiological processes overlap significantly with mechanisms implicated in the pathophysiology of depression, suggesting that psychedelics may target core biological disruptions associated with depressive symptomatology [18–21]. Recent evidence indicates that psychedelic-assisted interventions may not only provide symptomatic relief but also facilitate and support the psychotherapeutic process, by enhancing emotional openness, cognitive flexibility, and therapeutic alliance. This suggests that psychedelics could represent a valuable adjunct to psychotherapy in treatment-resistant depression and related conditions [22,23].

Research on psychedelics shows promising results, while also presenting methodological limitations related to protocol heterogeneity, blinding challenges and short follow-up periods, except for the 52-week COMP360 study [24]. An expanding body of clinical research has explored their safety, efficacy, and underlying mechanisms

of action, with promising preliminary results [25–27] Notably, a systematic review reported that approximately 79.2% of individuals diagnosed with unipolar mood disorders experienced clinical improvement following psychedelic-assisted therapy involving substances such as psilocybin, lysergic acid diethylamide (LSD) or mescaline [28]. However, these studies employed a wide range of dosing regimens, as well as variable therapeutic frameworks, making direct comparisons and standardization challenging. Despite these methodological differences, the therapeutic effects observed have contributed to a growing interest in the antidepressant potential of psychedelics

In particular, to date research on psilocybin continues to progress, with the FDA granting Breakthrough Therapy designation to several programs. Preliminary outcomes from phase 3 studies have already been published, while additional trials are presently underway to further validate these results. [29,30]. Recent studies also highlight sustained benefits of psilocybin in special populations, such as cancer patients with comorbid depression [31].

Furthermore, in recent years the clinical development of psychedelic therapies for mood disorders has expanded beyond psilocybin to include other short-acting tryptamines such as mebufotenin (5-MeO-DMT) and dimethyltryptamine (DMT), as well as LSD-based programs. Among these, 5-MeO-DMT currently presents the most advanced clinical evidence, with positive phase 2 trials in treatment-resistant depression (TRD) and planned Phase 3 studies. Early blinded trials have confirmed rapid onset, short session duration, and favorable tolerability profiles, supporting its potential scalability in clinical practice [29].

Beyond classic psychedelics, novel synthetic compounds such as bretisilocin (GM-2505) are emerging. Designed as a short-acting 5-HT2A agonist optimized for two-hour clinic workflows, bretisilocin has shown significant antidepressant effects in phase 2 studies [30].

Taken together, these developments illustrate a rapidly evolving therapeutic landscape, where classic and novel psychedelic agents are being actively investigated as innovative strategies for treatment-resistant and major depressive disorders.

1.3. Aim of the Study

TRD remains a complex and heterogeneous clinical condition, for which no universally accepted treatment algorithm currently exists. This literature review aims to examine the range of therapeutic strategies available for the management of TRD, with the overarching goal of contributing to the development of a more standardized and evidence-based clinical approach. By analyzing both established treatments and emerging interventions, the review seeks to clarify their clinical applicability, ultimately supporting more consistent, informed, and effective decision-making in the treatment of this challenging condition.

2. Materials and Methods

2.1. Data Source

We conducted a systematic search on 13 March 2025 using Pubmed and Scopus electronic databases and applying the following controlled vocabulary and keywords “(treatment resistant depression OR TRD) AND (glutamatergic OR glutamate OR psychedelic OR psilocybin OR antipsychotic augmentation) NOT (review OR animal OR mouse)”.

2.2. Inclusion and Exclusion Criteria

The exclusion criteria for both selection phases were: (1) non-original research (e.g., review, commentary, editorial, book chapter); (2) non full-text articles (e.g., meeting abstract); (3) language other than English; (4) animal/in vitro studies; (5) articles not deal with TRD; (6) articles not deal with glutamatergic treatments; (7) not dealing with psychedelic medications; (8) not dealing with antipsychotic augmentation. Finally, only articles published within the last 10 years were included. A total of 60 articles were included in the final analysis.

2.3. Data Extraction and Synthesis

A two-stage screening process was used. The selection and eligibility phase of the articles were carried out independently by CM, RA, SP, ADA, GiMa, LP, AS and after subjected to a last cross-check by AMo, CC, GdA, AMi and SC. All discordant cases will be evaluated by MP and GM. All authors reviewed and discussed preliminary results to reach consensus on the key findings.

3. Results

3.1. Overall Characteristics of the Studies Included

Among the included studies, the majority are observational studies (N = 20) [7,11,12,15,32–47], followed by randomized double-blind placebo-controlled trials (N = 19) [8,48–65], open label clinical trial (N = 5) [66–70], retrospective cohort studies (N = 4) [71–74], case reports (N = 3) [75–77], case series (N = 3) [78–80], pragmatic randomized clinical trial (N = 3) [81–83], pilot or phase I/II studies (N = 2) [84,85] and a qualitative interview study [86].

The total number of participants across all studies exceeds 205,000 patients, largely driven by three large population-based registry cohorts ([72], N = 177,144; [73], N = 20,478; [71], N = 5619). The remaining clinical trials and observational studies include smaller cohorts ranging from single case reports ([75], N = 1; [77], N = 1; [76], N = 1) to medium samples ([32], N = 30; [33], N = 36; [52], N = 99; [68], N = 676), and large pragmatic RCTs ([82], N = 742; [81], N = 396). Overall, the studies analyzed populations of adults aged 18 to 72 years, with the majority of participants diagnosed with unipolar TRD.

Regarding treatments, the most commonly studied intervention was intravenous racemic ketamine (N = 30) [12,32,34,35,37,41–46,48–55,59,60,62,63,65,69,70,74,75,86,87]. Oral or sublingual ketamine was tested in 2 studies [40,58], and sublingual troches in 1 study [77]. Intranasal esketamine was reported in 9 studies [7,11,15,33,68,76,78–80]. Subcutaneous esketamine was used in 1 study [60].

Augmentation strategies were evaluated in 10 studies [47,57,64,71–73,81–83,85].

Finally, psychedelics were investigated in 7 studies, including ayahuasca (N = 3) [39,56,61], psilocybin (N = 3) [36,38,67] and dimethyltriptamine (N = 1) [84].

3.2. Beyond Monoamines: The Glutamatergic Revolution in TRD

Glutamatergic agents, particularly ketamine and its enantiomer esketamine, have fundamentally transformed the treatment landscape for treatment-resistant depression by delivering rapid and robust antidepressant effects. A wealth of real-world and controlled studies has validated the efficacy of intravenous racemic ketamine administered at subanesthetic doses (0.5–1 mg/kg), often producing significant symptom improvement within hours after a single infusion [32–35,52,70]. Early investigations combining ketamine with electroconvulsive therapy (ECT) suggested a possible synergistic effect enhancing symptom remission [48]. Consistent reductions in Montgomery–Åsberg Depression Rating Scale scores have been reported in open-label studies across diverse clinical settings involving both unipolar and bipolar depression [37,43,49]. Neuroimaging research has further demonstrated rapid metabolic activation in prefrontal and subcortical brain circuits following ketamine infusion, correlating with clinical improvement [50,51,69].

Mechanistically, ketamine modulates the glutamatergic–GABAergic balance, influences kynurenine pathway metabolites, and affects systemic inflammatory markers, which collectively may underlie its antidepressant properties [42,59,63]. While case reports have documented rare adverse events such as mood switches or paradoxical symptom exacerbations, overall outcomes remain predominantly positive [75–77,80].

Ketamine-assisted psychotherapy (KAP), combining sublingual, intranasal, intramuscular or intravenous ketamine administration with structured psychotherapeutic sessions, has emerged as a comprehensive approach that yields sustained improvements in both depression and anxiety symptoms [40]. Long-term observational studies support the safety and clinical benefits of maintenance treatment protocols [55,74], with predictors of positive response including later age of depression onset and early symptomatic improvement [44,65], while factors like BMI and menopausal status appear to have minimal impact on outcomes [43,44].

Beyond clinical outcomes, pharmacometabolomic studies have identified broad neurochemical changes post-treatment, shedding light on rapid antidepressant mechanisms [60,62]. Genetic research suggests that specific polygenic risk profiles may influence treatment response, particularly regarding dissociative side effects and overall efficacy [41,86]. Additionally, neuroimaging and electrophysiological markers, such as increased EEG complexity, have been proposed as potential biomarkers predictive of response [54,55].

Protocols involving repeated ketamine infusions (typically six sessions over two to three weeks) are associated with enhanced and sustained antidepressant responses [12,46,70]. Extended infusions lasting up to 96 h have also been explored, resulting in durable remission for some TRD patients [69]. These protocols are generally well tolerated, with transient dissociation, hypertension, and nausea being the most commonly reported side effects [70,79].

On the other hand, intranasal esketamine, administered in doses ranging from 28 to 84 mg, has demonstrated significant reductions in depressive symptoms when used as an adjunct to oral antidepressants [7,11,15,68]. Esketamine offers a favorable tolerability profile and a lower risk of dissociation compared to racemic ketamine

[78,79]. Alternative formulations, including extended-release oral ketamine [58] and subcutaneous esketamine, show promise in enhancing treatment practicality and adherence without compromising efficacy [66].

In summary, evidence from these 43 studies, shown in Table 1, converges to highlight glutamatergic agents as a transformative advancement in managing TRD. In particular, they offer rapid-onset antidepressant effects through a unique glutamate-modulating mechanism and demonstrate promising safety profiles under clinical supervision.

Table 1. Findings on glutamatergic treatments.

	Agent and Administration	Key Findings
Agnorelli et al., 2025 [32]; Aust et al., 2019 [34]; Ballard et al., 2018 [35]; Fava et al., 2020 [52]; Singh et al., 2016 [70]	Racemic ketamine, IV (0.5–1 mg/kg, single or repeated infusions)	Rapid antidepressant effects within hours
McIntyre, 2021a [12]; McIntyre, 2021b [46]	Racemic ketamine, IV (6 infusions over 2–3 weeks)	Enhanced and sustained symptom improvement with repeated administration
Siegel, 2021 [69]	Racemic ketamine, prolonged IV (up to 96 h)	Durable remission in some patients with severe TRD
Altinay et al., 2019 [48]	Racemic ketamine + ECT, IV	Possible synergistic effect with ECT; improved remission rates
Chen et al., 2018 [50]; Chen et al., 2019 [49]; Chen, 2021 [37]; Li et al., 2016 [51]; Lipsitz, 2021 [45]; Lipsitz, 2021 [44]; Lipsitz, 2022 [43]; Kadriu et al., 2021 [59]; Kiraly et al., 2017 [42]; Singh, 2021 [63]; Banwari et al., 2015 [75]; Liester et al., 2024 [77]; Pennybaker, 2021 [74]; Murphy et al., 2023 [55]; Yonezawa et al., 2024 [65]; Rotroff et al., 2016 [60]; Saligan et al., 2016 [62]; Guo et al., 2018 [41]; Lapidos, 2023 [86]; Murrough et al., 2015 [53]; Murrough et al., 2015 [54]; Murrough et al., 2015 [87]	Racemic ketamine, various routes/settings; general mechanisms (IV, IM, oral, maintenance)	Consistent clinical efficacy in unipolar and bipolar depression; MADRS reduction; favorable safety profile; rare adverse events; neurobiological and genetic predictors of response; long-term benefit with maintenance protocols; EEG and metabolic biomarkers associated with clinical improvement
Dore et al., 2019 [40]	Racemic ketamine, IM or sublingual with psychotherapy (KAP)	Sustained reduction in depression and anxiety; benefit of combined psychotherapeutic framework
d'Andrea et al., 2024 [7]; Martinotti et al., 2022 [15]; Martinotti et al., 2023 [11]; Artin et al., 2022 [33]; Reif et al., 2023 [68]; Marcatili et al., 2021 [76]; Ontiveros-Sánchez de la Barquera et al., 2024 [80]	Esketamine, intranasal (28–84 mg)	Significant symptom reduction in adjunct to oral antidepressants
Fotiadis et al., 2024 [79]; Bentley, 2022 [78]	Esketamine vs. racemic ketamine, intranasal vs. IV	Esketamine shows lower dissociative potential
Glue et al., 2024 [58]	Ketamine, extended-release oral	Promising option for improved adherence with maintained efficacy
Palhano-Fontes et al., 2025 [66]	Esketamine, subcutaneous	Effective and practical route with favorable tolerability

Abbreviations: IV = intravenous; IM = intramuscular; ECT = electroconvulsive therapy; KAP = ketamine-assisted psychotherapy; MADRS = Montgomery–Åsberg Depression Rating Scale; EEG = electroencephalogram; TRD = treatment-resistant depression.

3.3. The Role of Antipsychotic Augmentation

TRD remains a major clinical challenge, often requiring augmentation strategies that involve the addition of adjunctive pharmacological agents. While antidepressant monotherapy and polypharmacy are still the most common approaches, a Finnish cohort study revealed that antipsychotics and mood stabilizers are used as augmentation in 15–24% of TRD cases—suggesting a shift toward more complex treatment regimens as the disorder persists [72]. Symptom severity plays a key role in guiding treatment decisions; in younger adults, the likelihood of receiving antipsychotic augmentation increases with greater depressive severity [73].

Among augmentation options, aripiprazole, an atypical antipsychotic, has been extensively studied, particularly in older adults. The pivotal OPTIMUM trial demonstrated that aripiprazole augmentation significantly improved psychological well-being compared to switching to bupropion, although both strategies showed similar remission rates [81,82]. On one hand, aripiprazole maintained a generally favorable safety profile, on the other hand bupropion was linked to a slightly higher incidence of falls.

In real-world settings, the ASCERTAIN-TRD trial compared three strategies: aripiprazole augmentation, repetitive transcranial magnetic stimulation (rTMS) augmentation, and switching antidepressants. While aripiprazole did not demonstrate statistical superiority over switching on the primary outcome, rTMS augmentation was found to

be more effective overall [83]. Supporting these findings, a Korean cohort study showed that bupropion augmentation was associated with a lower risk of depression-related hospitalization and movement disorders compared to aripiprazole—although these differences were not statistically significant in older adults [71]. The same study also reported comparative outcomes for quetiapine and olanzapine as augmentation agents, indicating higher rates of sedation and metabolic side effects with these agents, despite their modest efficacy [65].

Efforts to personalize augmentation strategies have identified several clinical predictors and potential biomarkers to optimize the use of atypical antipsychotics. Secondary analyses from the IRL-GRey trial suggested that certain baseline depressive features—such as pronounced sleep disturbances and less overt sadness—could predict a favorable response to aripiprazole [57]. Additionally, better cognitive flexibility (measured via set-shifting tasks) at baseline was associated with greater benefit from aripiprazole [85]. Integrative approaches that combine multiple clinical moderators have been proposed to construct more precise patient profiles, improving the likelihood of selecting the most effective treatment [64].

Finally, pharmacogenomic studies have explored genetic predictors of response to augmentation. A Japanese study specifically investigating the BDNF Val66Met polymorphism found no significant association with response to atypical antipsychotic augmentation, suggesting that the utility of current genetic markers in guiding augmentation strategies remains limited [47]. The key findings on the use of antipsychotics in TRD are summarized in Table 2.

Table 2. Findings from antipsychotic augmentation strategies.

	Therapeutic Agent and Administration	Key Findings
Lähteenvuo et al., 2022 [72]	Aripiprazole 2–10 mg/day, quetiapine 50–300 mg/day, olanzapine 5–10 mg/day, oral	Antipsychotic augmentation in 15–24% of TRD cases; reflects real-world practice
Lampela et al., 2023 [73]	Antipsychotics (ikely low-to-moderate dose atypicals), oral	More frequent use in younger adults with severe depression
Cristancho et al., 2019 [81]; Lenze et al., 2023 [82]	Aripiprazole starting at 2 mg/day, titrated to mean ~7 mg/day; compared to switch to bupropion (mean dose ~150–300 mg/day), oral	Aripiprazole improved well-being significantly; similar remission to bupropion; bupropion linked to slightly more falls
Gebara et al., 2017 [57]	Aripiprazole, average dose 6.6 mg/day, oral	Positive response linked to prominent sleep symptoms and low sadness at baseline
Kaneriya et al., 2016 [85]	Aripiprazole, mean dose ~6.5 mg/day, oral	Better response in patients with higher baseline cognitive flexibility (executive function)
Smagula et al., 2016 [64]	Atypical antipsychotics, including aripiprazole, risperidone (1–3 mg/day), quetiapine (100–300 mg/day), oral	Moderator-based treatment personalization showed promise for optimizing augmentation
Papakostas et al., 2024 [83]	Aripiprazole, dosing 2–10 mg/day vs. rTMS vs. antidepressant switch, oral	rTMS more effective than aripiprazole; aripiprazole not statistically superior to switching strategy
Lee et al., 2024 [71]	Aripiprazole, average dose 5 mg/day vs. bupropion 150–300 mg/day, oral	Bupropion associated with lower hospitalization and motor adverse effects, but differences not significant in elderly
Yoshimura et al., 2012 [47]	Olanzapine (5–10 mg/day), Risperidone (1–2 mg/day), Quetiapine (100–300 mg/day), Aripiprazole (2–10 mg/day), oral	No predictive value of BDNF Val66Met polymorphism for response to atypical antipsychotic augmentation

Abbreviations: TRD = treatment-resistant depression; rTMS = repetitive transcranial magnetic stimulation; BDNF = brain-derived neurotrophic factor.

3.4. The Therapeutic Promise of Psychedelics

Recent developments in psychopharmacology have increasingly focused on psychedelic compound. As promising new therapeutic options for treatment-resistant depression (TRD). A growing body of research not only supports their clinical effectiveness but also sheds light on the underlying neurobiological mechanisms driving their antidepressant effects.

Psilocybin has shown particularly strong potential. Early open-label studies reported rapid and sustained reductions in depressive symptoms, along with notable improvements in anxiety and anhedonia, all within a favorable safety profile [36]. These findings were later confirmed in a randomized clinical trial, which demonstrated that psilocybin-assisted psychotherapy (PAP) is both feasible and safe in complex TRD populations. The trial also highlighted a significant reduction in depression severity and suggested that repeated doses may offer cumulative benefits [67]. On a neurobiological level, individuals with lower baseline functional connectivity between the default mode network (DMN) and the salience network (SN) appeared to experience greater symptom improvement, suggesting a potential predictive biomarker for treatment response [38].

Ayahuasca, another plant-based psychedelic, has demonstrated antidepressant properties that may be mediated by both neuroplastic and immunoinflammatory mechanisms. A randomized controlled trial revealed a significant post-treatment rise in serum brain-derived neurotrophic factor (BDNF), a key protein involved in neural growth and plasticity [39]. Additional studies have linked ayahuasca's effects to decreases in elevated C-reactive protein (CRP) levels, a marker of systemic inflammation commonly seen in depressed individuals [56]. Moreover, in-depth analyses suggest that acute factors during the ayahuasca experience, such as immediate symptom relief and stable salivary cortisol levels, may act as moderators of improvements in key biological markers like BDNF and cortisol [61].

Dimethyltryptamine (DMT), known for its powerful but short-lived psychedelic effects, has also shown promise. In patients with major depressive disorder (MDD), intravenous DMT administration led to significant reductions in depression scores as early as the day following treatment, with minimal adverse effects and good overall tolerability [84].

Taken together these findings, shown in Table 3, highlight the potential of psychedelic-assisted therapies to reshape the treatment paradigm for TRD, offering both rapid symptom relief and a new window into the neurobiological underpinnings of depression.

Table 3. Findings from psychedelics agents**.**

	Therapeutic Agent and Administration	Key Findings
Carhart-Harris et al., 2016 [36]	Psilocybin, two oral doses: 10 mg (first session), then 25 mg (after 7 days), with psychological support	Rapid and sustained reductions in depression, anxiety, and anhedonia; excellent tolerability
Rosenblat et al., 2024 [67]	Psilocybin, oral doses of 25 mg, administered with psychotherapy in controlled setting	Safe and feasible in TRD; significant reduction in depression severity; repeated sessions show cumulative benefit
Copa et al., 2021 [38]	Psilocybin, oral dose 25 mg, fMRI analysis pre/post treatment	Lower DMN–SN connectivity at baseline predicted better symptom response
de Almeida et al., 2019 [39]	Ayahuasca, single dose (1 mL/kg)	Marked post-treatment increase in serum BDNF, supporting neuroplastic mechanisms
Galvão-Coelho et al., 2020 [56]	Ayahuasca, oral, single dose ~120–200 mL, standard brew	Reductions in CRP levels (inflammation marker); clinical improvement in depression symptoms
Sousa et al., 2022 [61]	Ayahuasca, oral, single session ~0.75–1.0 mg/kg	Acute symptom relief correlated with biomarker changes (BDNF, cortisol) and improved clinical outcomes
D'Souza et al., 2022 [84]	DMT, intravenous bolus: 0.1–0.4 mg/kg (average effective dose: 0.3 mg/kg)	Rapid reduction in depressive symptoms observed as early as 24 h post-treatment; minimal adverse effects

Abbreviations: TRD = Treatment-Resistant Depression; BDNF = Brain-Derived Neurotrophic Factor; CRP = C-Reactive Protein; DMN = Default Mode Network; SN = Salience Network; fMRI = Functional Magnetic Resonance Imaging; DMT = N,N-Dimethyltryptamine.

4. Discussion

The collective evidence from 60 studies included underscores the multifaceted and heterogeneous nature of TRD, while pointing toward promising paths through both established and emerging treatment modalities (Figure 1).

Our data suggest that, although there is increasing evidence in favor of combination therapies and augmentation strategies, traditional antidepressant approaches still dominate routine clinical practice [72,73]. However, pragmatic trials such as OPTIMUM [82] and IRL-GRey [57,85] have shown that augmentation with agents like aripiprazole or bupropion leads to superior outcomes in remission and functional recovery compared to switching antidepressants, particularly among older adults. Real-world observational data [71] reinforce these findings, further indicating that bupropion augmentation is linked to lower hospitalization rates and a more favorable side-effect profile than antipsychotic strategies, especially in terms of extrapyramidal symptoms.

Conversely, evidence from a recent systematic review indicates that emerging pharmacological agents, including brexpiprazole and cariprazine, demonstrate substantial potential as adjunctive therapies for TRD [88]. In particular, Brexpiprazole has been granted FDA approval as an adjunctive therapy to conventional oral antidepressants for major depressive disorder. This approval was based on the outcomes of pivotal randomized controlled trials, which demonstrated a statistically significant improvement in depressive symptoms among patients receiving brexpiprazole compared to placebo [89]. Similarly, cariprazine has shown promising results when evaluated as an adjunctive agent in MDD. Clinical studies have reported a significant reduction in depressive symptomatology, relative to placebo [86,87].

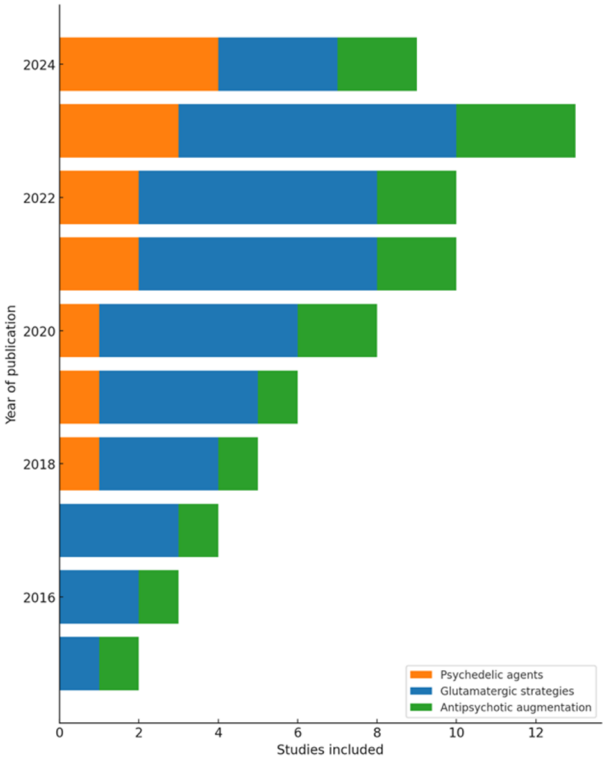

Figure 1. Map of therapeutic strategies measured by number of studies included**.**

Alongside these newer atypical antipsychotics, lurasidone has also gained attention for its efficacy in bipolar depression. Of relevance, a recent systematic review and meta-analysis by Aronica and colleagues confirmed the efficacy of lurasidone in the management of bipolar depression, with significant improvements reported in both depressive symptoms and functional disability [90]. Dose–response analyses further suggest that daily lurasidone doses of 40–60 mg optimally balance efficacy and safety, showing moderate effect sizes for depression, anxiety, global clinical impression, and disability, while minimizing adverse metabolic or endocrine effects. Notably, one of the key advantages of lurasidone is its relatively favorable side effect profile, particularly in terms of a lower propensity to cause metabolic disturbances and reduced levels of sedation [91]. These tolerability characteristics are clinically significant, especially in long-term management, as they may contribute to improved patient adherence and overall quality of life. Moreover, dose–response analyses have helped to refine the therapeutic positioning of lurasidone in bipolar depression [92].

Alongside this, the ongoing debate regarding the comparative efficacy of pramipexole augmentation versus atypical antipsychotics in treatment-resistant depression has gained new momentum. A randomized controlled trial demonstrated that pramipexole augmentation may provide benefits in unipolar depression [93], while the large placebo-controlled trial conducted in the UK confirmed its potential in treatment-resistant unipolar depression, showing promising though mixed results in the acute phase [94]. Importantly, the PAX-BD trial evaluated pramipexole as an adjunct to mood stabilizers in bipolar depression, reporting medium-sized but non-significant improvements at 12 weeks, with significant advantages observed at 36 weeks for some secondary outcomes including response, remission, and psychosocial functioning [95]. Together, these findings expand the therapeutic landscape and raise clinically relevant questions regarding the role of pramipexole compared with atypical antipsychotics in treatment-resistant depression.

Concurrently, the field has seen a paradigm shift driven by rapid-acting glutamatergic modulators, most notably intravenous ketamine, which has redefined expectations for response latency in TRD management. Our results show that ketamine, administered at subanesthetic doses (0.5–1 mg/kg), produces robust antidepressant effects within 24 to 72 h [52,87]. These effects are often sustained and enhanced with repeated infusions administered over 2–4 weeks, as shown in both controlled trials and real-world studies [33,34]. Neuroimaging data lend further support, revealing increased post-infusion cortical metabolism, particularly in the prefrontal cortex and anterior cingulate [51].

Intranasal esketamine has emerged as a similarly impactful innovation. Response and remission rates ranging from 60–70% and 30–50%, respectively, have been observed in real-world studies [7,11,15]. When combined with SSRIs, SNRIs, or vortioxetine, esketamine remains effective even in individuals with a long history of treatment

failure or bipolar depression [7,11,15]. Both ketamine and esketamine exhibit generally favorable safety profiles, with transient dissociation, mild sedation, and short-lived blood pressure increases being the most common side effects. Nonetheless, rare incidents of mania and paradoxical worsening of suicidal ideation highlight the need for careful patient screening [75].

Innovative formulations and delivery strategies are further improving the accessibility and utility of these treatments. Oral extended-release ketamine, investigated by Glue et al. [58], demonstrated dose-dependent efficacy over a 13-week period while minimizing dissociative effects. Additionally, ketamine-assisted psychotherapy (KAP), which integrates the neuroplastic benefits of ketamine with structured psychotherapeutic interventions, has broadened the therapeutic landscape. Large-scale retrospective studies have reported significant reductions in depression and anxiety, even in patients with complex trauma or borderline personality features, supporting the synergistic potential of combining pharmacological and psychotherapeutic approaches to facilitate long-term remission [40]. Recent studies suggest that combining ketamine with structured psychotherapeutic interventions may yield more durable clinical outcomes than ketamine infusion alone, particularly regarding sustained reductions in depressive symptoms and relapse prevention. For instance, evidence from PTSD research indicates that ketamine combined with trauma-focused psychotherapy produces longer-lasting symptom improvement than pharmacological treatment alone [96]. In addition, preliminary evidence in TRD suggests that cognitive behavioral therapy (CBT) administered after ketamine infusion may help sustain antidepressant effects over time [97]. This growing body of evidence underscores the added value of integrating psychotherapy into ketamine treatment protocols, aligning with a broader trend toward multimodal, personalized interventions in TRD.

Beyond glutamatergic modulation, serotonergic psychedelics are gaining traction as novel interventions for TRD. Ayahuasca has shown rapid antidepressant effects, potentially mediated through increased BDNF and reductions in inflammatory markers such as CRP and IL-6 [39,56]. Studies on psilocybin [36,38] suggest that resting-state functional connectivity between the salience network and default mode network may predict sustained antidepressant responses up to 24 weeks. Meanwhile, intravenous DMT has been found to produce moderate, short-lived antidepressant effects with good tolerability, warranting further large-scale trials [84].

Although pivotal trials are still ongoing and most indications remain unlicensed, several countries have already established controlled access to psychedelic therapies. Switzerland has long permitted case-by-case authorizations for psilocybin and MDMA [98], while Canada reinstated its Special Access Program in 2022 [99]. Australia became the first country to allow routine prescribing of psilocybin for TRD and MDMA for PTSD under strict regulation [100]. More recently, New Zealand, the Czech Republic, and Germany have also implemented limited clinical access pathways [101–103]. These developments show that real-world access, though tightly controlled, is progressing in parallel with ongoing pivotal trials. Furthermore, though still experimental, these psychedelic interventions signal a potential paradigm shift toward treatments that not only provide rapid symptom relief but also support enduring cognitive-emotional restructuring.

Finally, mechanistic and predictive insights emerging from these studies reinforce the value of precision psychiatry. Biomarker analyses have linked response to ketamine and esketamine with shifts in the kynurenine pathway, tryptophan metabolism, and phospholipid turnover [41,42]. Low baseline levels of fibroblast growth factor-2 (FGF2) have been associated with rapid remission following ketamine administration, and genomic studies are beginning to map individual differences in both treatment response and tolerability [42]. Additionally, EEG data reveal dynamic changes in brain complexity after ketamine infusion [55], although the clinical utility of these markers remains to be fully established.

From a clinical standpoint, early improvement during the first two ketamine sessions strongly predicts final treatment outcomes [44], though delayed responders are not uncommon. Notably, neither BMI nor menopausal status appears to significantly affect treatment response, suggesting that these emerging interventions are broadly applicable across diverse demographic groups.

Overall, the evolving landscape of TRD research reflects a shift toward more personalized, mechanism-based treatments. While traditional antidepressants remain central in clinical practice, the integration of rapid-acting agents, psychedelics, and biomarker-guided approaches represents a major advancement in addressing this complex and often refractory condition.

Implications for Clinical Practice

In practical terms, TRD treatment should follow a tiered, evidence-driven approach. Initial efforts should focus on optimizing existing antidepressant regimens, followed by pharmacological augmentation using agents like atypical antipsychotics.

For patients with persistent symptoms or acute risk, ketamine or esketamine, administered in a controlled clinical environment, can provide fast-acting relief and enhance functional recovery.

Pending further validation, psychedelic-assisted interventions may serve as options for the most refractory cases. Importantly, psychedelics may also contribute to the broader framework of precision psychiatry by leveraging their unique mechanisms of action—such as promoting neuroplasticity, enhancing emotional processing, and facilitating therapeutic alliance—to tailor interventions more closely to individual patient profiles.

Future developments could involve integrating psychedelic-assisted therapies with predictive biomarkers and neuroimaging markers of treatment response, thereby refining patient stratification and guiding personalized treatment selection.

5. Conclusions

This narrative review highlights the evolving landscape of TRD, emphasizing how advances in glutamatergic therapies, antipsychotic augmentation, and psychedelic-assisted interventions are reshaping both clinical practice and research priorities. The evidence supports a paradigm shift from traditional, sequential monotherapy toward a more dynamic, multimodal, and personalized treatment framework. Ketamine and esketamine have demonstrated rapid and robust antidepressant effects, particularly in acutely ill or high-risk patients, while antipsychotic augmentation remains a practical and evidence-based strategy for improving outcomes in partial responders. Psychedelics, though still investigational, offer novel mechanisms of action and may complement existing therapies by facilitating neuroplastic and emotional restructuring. Moving forward, integrating predictive biomarkers, structured treatment algorithms, and patient-centered care models will be essential to improve diagnostic precision, treatment efficacy, and long-term remission in TRD. Together, these developments signal a critical transition toward biologically informed, mechanism-based psychiatry that better addresses the complexity of depressive disorders and the needs of those who remain unresponsive to conventional approaches.

Author Contributions

Conceptualization: S.C. and C.C.; Methodology: S.C., A.M. (Alessio Mosca), G.d. and A.M. (Andrea Miuli); Data curation: G.d., C.C., G.T., C.M., R.A., S.P., A.D., G.M. (Giovanna Mammarella), L.P. and A.S.; Writing—original draft preparation: C.C., C.M., R.A. and S.P.; Writing—review and editing: S.C., C.C., G.d., A.M. (Alessio Mosca) and A.M. (Andrea Miuli); Supervision: G.M. (Giovanni Martinotti) and M.P. All authors have read and agreed to the published version of the manuscript.

Funding

This study was not supported by any sponsor or funder.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Conflicts of Interest

Given their editorial roles, Giovanni Martinotti (Editor-in-Chief) and Stefania Chiappini (Associate Editor) had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

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