International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	MODERN STRATEGIES FOR THE TREATMENT OF TREATMENT-RESISTANT DEPRESSION – A LITERATURE REVIEW
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3822
RECEIVED	29 July 2025
ACCEPTED	28 September 2025
PUBLISHED	30 September 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

© The author(s) 2025.
This article is published as open access under the Creative Commons Attribution 4.0 International License (CC BY 4.0), allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

MODERN STRATEGIES FOR THE TREATMENT OF TREATMENT-RESISTANT DEPRESSION – A LITERATURE REVIEW

Ignacy Rożek *(Corresponding Author, Email: ignacy-rozek@o2.pl)*
Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, Lublin, Poland
ORCID ID: 0009-0005-5731-6983

Wojciech Gąska
Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, Lublin, Poland
ORCID ID: 0009-0005-7621-3533

Izabela Lekan
St. John Paul II Provincial Hospital in Siedlce, Siedlce, Poland
ORCID ID: 0009-0000-5079-9795

Joanna Mazurek
1st Military Clinical Hospital with Polyclinic SPZOZ in Lublin, Lublin, Poland
ORCID ID: 0009-0005-0300-7798

Agnieszka Brzezińska
Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, Lublin, Poland
ORCID ID: 0000-0001-5730-8813

Weronika Tuszyńska
University Clinical Center of the Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0000-0002-2395-6748

Alicja Sodolska
Ophthalmology s.c. Primary Care Clinic, Lublin, Poland
ORCID ID: 0009-0008-3689-7004

Michał Lenart
University Clinical Hospital No. 1 in Lublin, Lublin, Poland
ORCID ID: 0009-0006-5103-7251

Barbara Madoń
Medical University of Lublin, Lublin, Poland
ORCID ID: 0000-0003-1054-6405

Barbara Teresińska
Medical University of Lublin, Lublin, Poland
ORCID ID: 0000-0002-1101-3566

ABSTRACT

Treatment-resistant depression (TRD) remains a major therapeutic challenge in psychiatry, affecting a substantial proportion of individuals diagnosed with major depressive disorder and contributing significantly to the overall burden of mental illness. Despite decades of research and the availability of numerous antidepressant agents, many patients fail to achieve full remission, which underscores the urgent need for more effective interventions. This review provides a comprehensive and up-to-date analysis of both established and novel strategies for the management of TRD, encompassing pharmacological augmentation approaches, a variety of neuromodulation techniques, the clinical application of psychedelic- assisted therapies, and the development of innovative compounds currently under investigation. Particular emphasis is placed on the therapeutic potential and clinical outcomes associated with ketamine, esketamine, and psilocybin, which have emerged as promising options for patients who do not respond to conventional treatments. In addition, the review explores future directions in TRD management, including the repurposing of agents such as lurasidone, pioglitazone, and minocycline, which may offer new mechanisms of action and improved tolerability. Finally, the discussion highlights the importance of adopting a personalized, evidence-based, and multidimensional treatment approach, with the goal of improving both short-term response rates and long-term functional recovery in individuals suffering from TRD.

KEYWORDS

Treatment-Resistant Depression, Ketamine, Esketamine, Psilocybin, Neuromodulation, Emerging Therapies, Augmentation

CITATION

Ignacy Rożek, Wojciech Gąska, Izabela Lekan, Joanna Mazurek, Agnieszka Brzezińska, Weronika Tuszyńska, Alicja Sodolska, Michał Lenart, Barbara Madoń, Barbara Teresińska. (2025). Modern Strategies for the Treatment of Treatment-Resistant Depression – A Literature Review. *International Journal of Innovative Technologies in Social Science*, 3(47). doi: 10.31435/ijitss.3(47).2025.3822

COPYRIGHT

© The author(s) 2025. This article is published as open access under the **Creative Commons Attribution 4.0 International License (CC BY 4.0)**, allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

Introduction

Major depressive disorder is a leading cause of disability worldwide. Despite advances in pharmacotherapy, a substantial subset of patients fails to achieve remission with standard treatments—referred to as treatment-resistant depression (TRD). The complexity of TRD requires multidimensional therapeutic strategies that address neurobiological, psychological, and inflammatory factors. In recent years, innovative treatments including glutamatergic agents, psychedelics, and repurposed medications have reshaped the therapeutic landscape.

Aim of the Study

The aim of this study is to review the current evidence for the management of TRD, with a focus on established, novel, and investigational therapies. The objective is to provide clinicians with a detailed overview of treatment options supported by contemporary clinical and mechanistic data.

Materials and Methods

This narrative review is based on an analysis of peer-reviewed literature, including randomized controlled trials, meta-analyses, and mechanistic studies concerning the treatment of TRD. Sources were collected from databases such as PubMed, and included both landmark and recent publications. Particular emphasis was placed on studies related to augmentation strategies, neuromodulatory techniques, ketamine and esketamine use, psychedelic interventions, and emerging pharmacological agents.

Conclusion

TRD continues to pose a formidable clinical problem, demanding innovative and individualized approaches. While traditional augmentation strategies and neuromodulation retain clinical value, novel interventions such as ketamine, esketamine, and psilocybin demonstrate significant promise. Additionally, repurposed and emerging agents targeting inflammation and neuroplasticity may broaden therapeutic possibilities. The evolving treatment paradigm for TRD necessitates further rigorous research to guide evidence-based practice and improve long-term outcomes for affected individuals.

Chapter 1: The Problem of Treatment-Resistant Depression

Depression is one of the most common mental disorders globally, affecting over 300 million people, and is a leading cause of disability and premature mortality (Kajumba et al., 2024). Despite significant advances in antidepressant pharmacotherapy in recent decades, a substantial portion of patients fail to achieve meaningful clinical improvement. It is estimated that up to 60% of patients do not improve after the first treatment trial (Kajumba et al., 2024), and approximately 30% develop treatment-resistant depression (TRD) (Kajumba et al., 2024) (Steffens, 2024)

TRD is most commonly defined as failure to achieve remission despite adequate trials of at least two antidepressant treatments at appropriate dosages and durations (Steffens, 2024), (Pandarakalam, 2018). However, there is no universally accepted definition, leading to discrepancies in prevalence estimates and complicating the creation of consistent therapeutic guidelines (Pandarakalam, 2018), (Zhdanava et al., 2021)

TRD has serious consequences for both patients and healthcare systems. Patients with TRD experience significantly reduced quality of life, higher levels of psychological distress, more frequent hospitalizations, and markedly increased healthcare costs (Naguy et al., 2023). In the United States alone, TRD is estimated to account for over $43 billion annually, nearly half of the total costs associated with depression treatment (Naguy et al., 2023).

A major obstacle in managing TRD is the absence of clear biomarkers that could identify depression subtypes or predict treatment response. As a result, the dominant therapeutic model remains trial-and-error, often leading to frustration for both patients and clinicians (Kajumba et al., 2024), (Pandarakalam, 2018)

Neurobiologically, TRD involves a complex interplay of regulatory systems, including the monoaminergic pathways (serotonergic, noradrenergic, and dopaminergic), the

hypothalamic-pituitary-adrenal (HPA) axis, neuroinflammatory processes, and genetic factors (Kajumba et al., 2024). Notably, the dopaminergic system is considered crucial, especially in relation to anhedonia and motivational deficits typical of TRD (Kajumba et al., 2024). It has been shown that long-term SSRI therapy may induce so-called emotional blunting in a significant proportion of patients (Kajumba et al., 2024). Dopamine deficiency may be both a consequence of medication and a perpetuating factor in resistance.

The role of neuroinflammation in TRD is supported by numerous studies. Elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β are associated with reduced dopaminergic activity and poorer treatment response (Kajumba et al., 2024). Moreover, the activation of the kynurenine pathway—shifting tryptophan metabolism away from serotonin production and toward neurotoxic metabolites—has also been implicated (Diaz et al., 2022).

TRD affects not only adults, but also older patients (Steffens, 2024) and adolescents (Naguy et al., 2023). In geriatric populations, comorbid medical conditions often complicate treatment optimization, and TRD prevalence may exceed 40% (Steffens, 2024). Among younger patients, no uniform definition of TRD exists, and there is a lack of high-quality studies assessing treatment efficacy in this group (Naguy et al., 2023).

Current therapeutic approaches include dose optimization, switching antidepressants, augmentation, psychotherapy, and biological treatments such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and ketamine therapy (Kajumba et al., 2024), (Caldiroli et al., 2021),(Pandarakalam, 2018). There is growing interest in glutamatergic agents and psychedelic compounds such as esketamine and psilocybin, which demonstrate rapid onset of action and efficacy in patients unresponsive to conventional treatments (Kajumba et al., 2024), (Caldiroli et al., 2021). In research on treatment-resistant bipolar depression (TRBD), agents such as lurasidone, D-cycloserine, pioglitazone, minocycline, N-acetylcysteine, renin-angiotensin system modulators, and anti-inflammatory agents like celecoxib are under investigation (Diaz et al., 2022).

Treatment-resistant depression remains a major clinical and public health challenge. Understanding its biological complexity and developing individualized treatment strategies are among the most pressing tasks in modern psychiatry.

Chapter 2: Dose Optimization, Antidepressant Switching, and Augmentation in Treatment-Resistant Depression

The management of treatment-resistant depression (TRD) presents a significant clinical challenge and requires the individualization of therapeutic strategies. Three core pharmacological approaches are typically employed: dose optimization of antidepressants, switching antidepressant agents, and augmentation—adding an additional agent to the current treatment.

2.1 Optimization of Antidepressant Treatment

The initial step in the absence of a treatment response is ensuring that an appropriate antidepressant has been used at an adequate dose and for a sufficient duration. The minimum treatment period necessary to evaluate efficacy is typically 6–8 weeks, but can extend to 12 weeks in some cases (Philip et al., 2010). The dose should reach at least two-thirds of the maximum recommended by the manufacturer, though in clinical practice, further increases are often required (Philip et al., 2010).

In some cases, therapeutic drug monitoring can be beneficial, particularly with tricyclic antidepressants (TCAs), where a clear relationship exists between plasma concentration and clinical response (Philip et al., 2010). Ensuring patient compliance is equally critical, as non- adherence is a common cause of apparent treatment resistance (Philip et al., 2010).

2.2 Switching Antidepressants

If optimization fails, switching to another antidepressant is the next step. This may involve an intraclass switch (e.g., from one SSRI to another), which is often well tolerated and allows for quick transition (Philip et al., 2010). Alternatively, switching across classes (e.g., from an SSRI to an SNRI, TCA, bupropion, or mirtazapine) may offer slightly higher efficacy in some cases (Philip et al., 2010).

In the STAR*D trial, during the second treatment stage, patients who did not respond to citalopram were switched to sertraline (within-class), venlafaxine, or bupropion (across- class). A modest increase in remission rates (3–7%) was observed regardless of the strategy used (Philip et al., 2010).

2.3 Antidepressant Augmentation

Augmentation involves adding a new agent to the current antidepressant regimen without discontinuing the primary medication. Research suggests that augmentation may be more effective than switching, particularly when agents with different mechanisms of action are combined (Nuñez et al., 2022), (Moret, 2005), (Philip et al., 2010).

Common augmentation strategies include:

Lithium: One of the most thoroughly studied agents for augmentation, especially effective when combined with TCAs, SSRIs, or SNRIs (Moret, 2005).

Thyroid hormones (e.g., T3): Often used to augment SSRIs, these can enhance treatment efficacy in resistant cases (Philip et al., 2010).

Second-generation antipsychotics (e.g., aripiprazole, quetiapine, olanzapine): Frequently used to augment SSRIs, with strong evidence supporting their efficacy in clinical settings (Nuñez et al., 2022),(Moret, 2005),(Philip et al., 2010).

Additional augmentation options include lamotrigine, carbamazepine, valproates (mood stabilizers), bupropion (a norepinephrine-dopamine reuptake inhibitor), and mirtazapine (with adrenergic and serotonergic activity) (Moret, 2005).

Several augmentation strategies aim to target multiple neurotransmitter systems simultaneously. For instance, combining an SSRI (e.g., fluoxetine) with desipramine allows concurrent stimulation of serotonergic and noradrenergic pathways (Moret, 2005). Similarly, the combination of venlafaxine and mirtazapine—known as the "California rocket fuel" strategy—targets serotonergic, noradrenergic, and dopaminergic systems (Moret, 2005).

Studies have also shown that compounds with atypical mechanisms, such as S- adenosylmethionine (SAMe), may be effective adjuncts to conventional antidepressants (Moret, 2005). S-adenosylmethionine is an endogenous methyl donor that modulates key neurotransmitter systems involved in depression, including serotonergic, dopaminergic, and noradrenergic pathways. It enhances monoamine turnover, promotes BDNF expression, and influences methylation-dependent neurochemical processes. Clinical studies suggest that SAMe, when used as adjunctive therapy, may accelerate and augment antidepressant response in treatment-resistant depression, with a favorable tolerability profile (Cuomo et al., 2020).

Chapter 3: The Role of Psychotherapy in the Treatment of Treatment-Resistant Depression

Psychotherapy is a crucial but often underutilized component in the management of treatment-resistant depression (TRD). While pharmacological strategies remain the mainstay of first-line treatment, a significant proportion of patients do not respond adequately to medications alone, highlighting the need for integrative therapeutic approaches. Among the available modalities, evidence-based psychotherapies—particularly cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and mindfulness-based cognitive therapy (MBCT)—have shown efficacy both as standalone treatments and as adjuncts to pharmacotherapy (Gałecki & Bliźniewska-Kowalska, 2021), (Hicks et al., 2010).

The inclusion of psychotherapy in TRD management is increasingly supported by national and international treatment guidelines. Both the American Psychiatric Association and the American Psychological Association recommend the use of structured psychotherapies in depression treatment, including for patients with treatment-resistant forms (Gałecki &Bliźniewska-Kowalska, 2021). These interventions are manualized, empirically supported, and tailored to address core features of depression, such as cognitive distortions, interpersonal dysfunction, and maladaptive behavioral patterns.

A 2021 meta-analysis involving over 34,000 patients with major depression showed that structured psychotherapies, including CBT, IPT, problem-solving therapy, behavioral activation, and supportive counseling, were significantly more effective than usual care or waiting list control in reducing depressive symptoms (Gałecki & Bliźniewska-Kowalska, 2021). Notably, when psychotherapy was combined with pharmacotherapy, response and remission rates were higher than for either approach alone (Gałecki & Bliźniewska- Kowalska, 2021), (Rush, 2023). The therapeutic alliance formed through regular and collaborative sessions may also enhance treatment adherence and improve outcomes (Gałecki & Bliźniewska-Kowalska, 2021).

CBT is the most extensively studied psychotherapy for TRD and is particularly effective in addressing persistent negative beliefs and behavioral avoidance. Techniques such as behavioral activation and thought restructuring help patients regain a sense of agency and motivation (Karrouri et al., 2021). Additionally, CBT has demonstrated long-term efficacy in relapse prevention, making it an ideal intervention for patients who have achieved partial response with pharmacological agents.

Interpersonal therapy (IPT) is another validated approach, particularly beneficial for patients whose depressive symptoms are closely linked to interpersonal conflicts or role transitions. IPT aims to improve communication skills, strengthen social support networks, and enhance the patient's ability to navigate relational stressors, which may otherwise perpetuate depressive episodes (Hicks et al., 2010), (Karrouri et al., 2021).

More recent developments include computerized CBT (cCBT) and guided self-help programs, which offer scalable and accessible alternatives for patients with logistical or economic barriers to in-person therapy. These digital interventions have shown promise in clinical trials, particularly when supported by therapist guidance (Hicks et al., 2010).

The exclusion of psychotherapy from TRD definitions may be a significant oversight. Many patients labeled as treatment-resistant may not have received adequate trials of evidence- based psychotherapy (Gałecki & Bliźniewska-Kowalska, 2021), (Rush, 2023). Furthermore, nonadherence to pharmacotherapy is often mistakenly interpreted as resistance; in such cases, supportive psychotherapy may play a critical role in addressing motivational barriers and fostering engagement with the treatment plan (Gałecki & Bliźniewska-Kowalska, 2021).

Chapter 4: Electroconvulsive Therapy in Treatment-Resistant Depression

Electroconvulsive therapy (ECT) remains one of the most effective somatic treatments available for patients with treatment-resistant depression (TRD). Despite its controversial image and declining use in some settings, numerous studies have confirmed its superiority over pharmacological interventions in severe, chronic, and resistant forms of depression (Kritzer et al., 2023).

ECT is indicated particularly in cases of severe major depressive disorder with psychotic features, suicidal ideation, catatonia, or a lack of response to multiple antidepressant trials [16]. In TRD, ECT can provide a rapid and substantial reduction in depressive symptoms, often after only a few sessions, making it a crucial option in life-threatening clinical scenarios (Kajumba et al., 2024), (Kritzer et al., 2023).

The mechanism of action of ECT is multifactorial and remains not fully understood. It involves neuroplastic changes, neuroendocrine modulation, and normalization of dysfunctional neural networks. Evidence suggests that ECT affects multiple neurotransmitter systems, including serotonergic, noradrenergic,

dopaminergic, and glutamatergic pathways, as well as enhancing brain-derived neurotrophic factor (BDNF) expression and hippocampal neurogenesis (Kritzer et al., 2023).

The clinical efficacy of ECT has been demonstrated in both unipolar and bipolar depression. Studies show that response rates in TRD patients treated with ECT may exceed 60–80%, significantly outperforming pharmacotherapy alone (Caldiroli et al., 2021), (Kritzer et al., 2023). Moreover, ECT is particularly effective in older adults and those with melancholic or psychotic features, groups that often show poor responses to antidepressants (Steffens, 2024), (Kritzer et al., 2023).

While ECT is a powerful tool, its application requires careful consideration of side effects and patient preferences. The most commonly reported adverse effects include transient cognitive impairments, especially memory disturbances. However, modern ECT techniques—such as right unilateral ultra-brief pulse stimulation—have significantly reduced cognitive side effects without compromising efficacy (Kritzer et al., 2023). Informed consent and patient education are essential to reduce stigma and foster acceptance of ECT as a legitimate and evidence-based treatment option.

Maintenance therapy following a successful ECT course is critical to prevent relapse. This may include continuation ECT (e.g., weekly or biweekly sessions), pharmacotherapy, or a combination of both (Kritzer et al., 2023). Without adequate maintenance, relapse rates within six months post-ECT can be as high as 50%–80% (Kritzer et al., 2023).

Despite its high efficacy, ECT remains underutilized due to stigma, misconceptions, logistical barriers, and limited access in certain healthcare systems. Increasing clinician awareness, improving infrastructure, and addressing public misconceptions are necessary steps to integrate ECT more broadly into TRD treatment algorithms (Kajumba et al., 2024), (Kritzer et al., 2023).

Chapter 5: Transcranial Magnetic Stimulation in Treatment-Resistant Depression

Transcranial magnetic stimulation (TMS) is a non-invasive neurostimulation technique that has emerged as a valuable treatment option for patients with treatment-resistant depression (TRD). Approved by the FDA in 2008 for major depressive disorder (MDD), TMS uses rapidly alternating magnetic fields to induce electrical currents in the prefrontal cortex, modulating brain circuits implicated in mood regulation (Conelea et al., 2017).

TMS is typically administered as repetitive TMS (rTMS) over the left dorsolateral prefrontal cortex (DLPFC), an area associated with hypoactivity in depression. High-frequency stimulation (typically 10 Hz) has been shown to produce antidepressant effects through neuroplastic changes, increased cerebral blood flow, and modulation of cortical excitability (Conelea et al., 2017). More recent approaches include theta-burst stimulation (TBS), which delivers patterned stimulation in a shorter time frame while maintaining clinical efficacy (Croarkin et al., 2021).

Clinical trials and meta-analyses have consistently demonstrated that TMS is superior to sham treatment in reducing depressive symptoms, particularly in patients who have not responded to at least one adequate trial of antidepressant therapy. Remission and response rates vary depending on treatment parameters and patient characteristics, but average remission rates range from 20–30%, with response rates of 40–50% (Conelea et al., 2017), (Croarkin et al., 2021).

TMS is generally well tolerated, with the most common side effects being scalp discomfort and transient headache. Unlike electroconvulsive therapy (ECT), TMS does not require anesthesia or induce seizures, making it a preferred option for patients concerned about cognitive side effects (Kritzer et al., 2023), (Conelea et al., 2017).

The therapeutic efficacy of TMS has been confirmed in diverse populations, including older adults. A naturalistic study comparing outcomes in patients younger and older than 60 years found no significant differences in remission or response rates, suggesting that age should not be a limiting factor in TMS eligibility (Conelea et al., 2017). In fact, both groups showed significant symptom reductions, and TMS was well tolerated regardless of age. This challenges earlier concerns about reduced efficacy in geriatric populations due to factors such as cortical atrophy or comorbidities (Conelea et al., 2017).

Importantly, TMS has also shown promise as a safe and feasible option for pregnant women with MDD who face high decisional conflict regarding pharmacologic treatment. In a randomized controlled trial, TMS administered during the second and third trimesters resulted in significant reductions in depressive symptoms compared to sham treatment, without notable adverse effects on maternal or fetal outcomes. Hormonal levels (estradiol, progesterone) remained stable, and no cognitive impairments were observed in mothers, highlighting the potential of TMS as a non-pharmacological alternative in this vulnerable population (Kim et al., 2019).

The mechanism of TMS is thought to involve alterations in synaptic plasticity, modulation of neurotransmitter systems (including glutamate, GABA, and dopamine), and downstream effects on limbic and subcortical structures. Neuroimaging studies support changes in functional connectivity following TMS, correlating with clinical improvements in depressive symptoms (Conelea et al., 2017).

Although TMS is increasingly incorporated into treatment guidelines for TRD, it remains underutilized due to limited access, high cost, and insufficient awareness among clinicians. Further research is needed to refine stimulation parameters, identify biomarkers of response, and explore synergistic combinations with pharmacotherapy or psychotherapy (Croarkin et al., 2021).

Chapter 6: Ketamine and Esketamine in Treatment-Resistant Depression

6.1 Ketamine

Ketamine, a racemic mixture containing R- and S-enantiomers, has emerged as a rapid-acting antidepressant with transformative potential in treatment-resistant depression (TRD). Unlike conventional monoaminergic antidepressants, which often require weeks to take effect, ketamine can produce rapid antidepressant effects within hours, making it particularly valuable for patients in acute suicidal crisis or with severe symptomatology (Yavi et al., 2022), (Nikolin et al., 2023).

Its primary mechanism involves antagonism of the N-methyl-D-aspartate receptor (NMDAR), a critical component of the glutamatergic system. This blockade leads to increased glutamate release and subsequent AMPA receptor activation. The downstream effects include increased brain-derived neurotrophic factor (BDNF) and activation of the mammalian target of rapamycin (mTOR) pathway, which facilitates synaptogenesis and reverses stress-induced neuronal atrophy (Nikolin et al., 2023), (McIntyre et al., 2021), (Borbély et al., 2022).

The standard protocol involves intravenous administration of ketamine at 0.5 mg/kg over 40 minutes, though higher doses up to 1.0 mg/kg have also been studied (Gałecki et al., 2024). Numerous randomized controlled trials (RCTs) have demonstrated response rates exceeding 50%, with remission rates around 30% in TRD patients (Yavi et al., 2022), (Halpape et al., 2025), (Jagtiani, 2024). A large meta-analysis revealed higher efficacy of intravenous racemic ketamine compared to intranasal esketamine, both in terms of response and remission rates, and with fewer treatment discontinuations (Jagtiani, 2024), (Gałecki et al., 2024).

Ketamine is metabolized predominantly by CYP2B6 and CYP3A4 enzymes into active metabolites, including (2R,6R)-hydroxynorketamine, which may contribute significantly to its antidepressant effect (Gałecki et al., 2024). The route of administration affects both bioavailability and tolerability—while intravenous ketamine has nearly 100% bioavailability, intranasal and oral routes vary widely, often between 10–50% (Gałecki et al., 2024).

Notably, recent studies have explored the feasibility and safety of intranasal racemic ketamine for maintenance therapy in outpatient settings. A small-scale naturalistic study reported stable or improved symptoms and quality of life over six months of outpatient intranasal therapy, with a good safety profile and no serious adverse events (Halpape et al., 2025). Though limited in sample size, these findings suggest that intranasal racemic ketamine may be a viable long-term option for select patients.

The use of ketamine in special populations such as adolescents, elderly individuals, and patients with bipolar depression also warrants consideration. Ketamine has demonstrated efficacy in both unipolar and bipolar depression, with low risk of inducing mania when mood stabilizers are co-administered (Gałecki et al., 2024). However, clinicians should remain cautious, particularly in patients with comorbid cluster B personality disorders or a history of substance use.

Overall, ketamine represents a paradigm shift in the treatment of TRD, offering rapid symptom relief and a novel mechanistic approach that extends beyond the monoaminergic paradigm (Jagtiani, 2024).

6.2 Esketamine

Esketamine, the S-enantiomer of ketamine, was developed as a more selective and accessible agent for TRD treatment. It exhibits higher affinity for the NMDAR and is administered intranasally, increasing convenience for outpatient use. Approved by the FDA in 2019 and regulated under the Risk Evaluation and Mitigation Strategy (REMS) program, esketamine must be administered in a certified setting under supervision (Nikolin et al., 2023), (Vasiliu, 2023), (Aust Prescr, 2022).

The bioavailability of intranasal esketamine ranges between 30–50%, with peak plasma concentrations typically reached within 20–40 minutes. It undergoes hepatic metabolism via cytochrome P450 enzymes,

primarily CYP2B6 and CYP3A4, and its elimination half-life is approximately 5 hours—longer than racemic ketamine (Aust Prescr, 2022), (Gałecki et al., 2024).

Treatment typically involves co-administration with an oral antidepressant. Induction starts with 56 mg twice weekly, followed by either 56 mg or 84 mg once weekly or biweekly during maintenance, depending on the clinical response (Vasiliu, 2023), (Borbély et al., 2022). Clinical trials and meta-analyses have shown significant improvements in Montgomery–Åsberg Depression Rating Scale (MADRS) scores with esketamine versus placebo, with rapid onset of action often within hours (Daly et al., 2018), (Jalloh, 2020).

Despite its efficacy, esketamine may be less effective than racemic ketamine overall. Meta- analyses comparing both compounds report higher response and remission rates for racemic ketamine, with fewer dropouts due to adverse effects (Jagtiani, 2024), (Gałecki et al., 2024). However, esketamine remains the only agent officially approved for TRD in both the US and EU, and its utility as a controlled, standardized outpatient treatment remains critical (Jagtiani, 2024), (Borbély et al., 2022).

Esketamine's side effects include transient dissociation, dizziness, elevated blood pressure, sedation, and perceptual disturbances. Due to the risk of hypertensive crises, blood pressure must be closely monitored before and after administration (Aust Prescr, 2022), (Jalloh, 2020). While its abuse potential is lower than that of ketamine, caution is advised in individuals with a history of substance use disorders (Aust Prescr, 2022).

Research continues into esketamine's role as an augmentation therapy and its neuroplastic effects. Its mechanism of action, involving NMDAR antagonism and downstream mTOR and BDNF activation, overlaps with racemic ketamine. However, further head-to-head trials are needed to clarify relative efficacy and tolerability profiles (Jagtiani, 2024).

In summary, despite its logistical and financial burdens, esketamine constitutes a major advancement in the management of TRD, bridging the gap between conventional pharmacotherapy and more invasive approaches such as ECT (Vasiliu, 2023), (Borbély et al., 2022).

6.3 Psilocybin

Psilocybin, a naturally occurring serotonergic psychedelic compound, has emerged as a novel intervention for major depressive disorder (MDD), including TRD. Acting primarily as a serotonin 2A receptor (5-HT2A) agonist, psilocybin induces alterations in perception, cognition, and self-processing, and appears to reset dysfunctional brain networks implicated in depression (Carhart-Harris et al., 2018), (Dougherty et al., 2023).

Clinical interest in psilocybin therapy intensified following several trials demonstrating rapid and sustained reductions in depressive symptoms after one or two supervised administrations. In an open-label study by Carhart-Harris et al. (2016), patients with TRD received two doses of psilocybin (10 mg and 25 mg one week apart), leading to significant symptom reduction lasting up to 3 months (Dougherty et al., 2023), (Carhart-Harris et al., 2016). No serious adverse events were reported, and the treatment was well tolerated, with transient side effects such as anxiety and nausea (Carhart-Harris et al., 2016).

Functional MRI data from these studies revealed decreased blood flow in the medial prefrontal cortex and amygdala, coupled with increased functional connectivity within the default mode network (DMN) post-treatment, suggesting normalization of brain function associated with mood regulation (Agin-Liebes & Davis, 2022), (Carhart-Harris et al., 2016).

Randomized controlled trials further supported the antidepressant potential of psilocybin. A landmark study showed that a single high-dose session with psychological support led to significant reductions in depression scores, with over half of participants reaching remission at one month (Carhart-Harris et al., 2018). Psilocybin also demonstrated comparable or superior outcomes to SSRIs in head-to-head comparisons, with a favorable side-effect profile and rapid onset of action (Borissova & Rucker, 2024).

Mechanistically, psilocybin-induced experiences often involve mystical-type states and emotional breakthroughs, which may facilitate reprocessing of traumatic or maladaptive cognitive patterns. Integration therapy following the psychedelic session helps patients derive lasting insights and behavior change from the experience (Carhart-Harris et al., 2018), (Agin- Liebes & Davis, 2022).

Due to these promising results, psilocybin has received "Breakthrough Therapy" designation from the FDA, promoting expedited development. However, its use remains experimental and is restricted to clinical trials or controlled settings in most countries (Carhart-Harris et al., 2018), (Carhart-Harris et al., 2016).

Chapter 7: Emerging Therapies in Treatment-Resistant Depression

Despite the availability of pharmacological and neuromodulatory strategies for treatment- resistant depression (TRD), a significant subset of patients continues to experience refractory symptoms. Therefore, novel and repurposed agents are under investigation. This chapter presents several promising future therapies for TRD, each discussed in a dedicated subsection.

7.1 Lurasidone

Lurasidone is an atypical antipsychotic approved for bipolar depression and schizophrenia, now being investigated as an adjunctive agent in unipolar TRD. Functioning as a serotonin- dopamine antagonist, lurasidone also exhibits partial agonism at 5-HT1A receptors and antagonism at 5-HT7 receptors. These pharmacodynamic properties are hypothesized to contribute to its antidepressant effects (Chiu & Chang, 2025).

An open-label pilot study evaluated the safety and efficacy of adjunctive lurasidone in TRD. Seventeen patients received lurasidone in addition to their current antidepressant regimen.

Over eight weeks, patients demonstrated significant improvements in Montgomery–Åsberg Depression Rating Scale (MADRS) scores, with minimal adverse effects reported (Chiu & Chang, 2025). Although the sample was small, the results suggest that lurasidone may provide benefit in TRD, warranting larger controlled trials.

7.2 D-Cycloserine

D-cycloserine (DCS), a partial agonist at the glycine site of the NMDA receptor, has drawn attention for its role in enhancing cognitive-behavioral therapies and modulating neuroplasticity. In TRD, it may support antidepressant effects through modulation of glutamatergic neurotransmission (Heresco-Levy et al., 2013).

In preclinical studies, DCS enhanced antidepressant-like behavior in rodent models. While initial clinical findings in depression are limited and mixed, DCS has been shown to accelerate the onset of antidepressant effects when combined with SSRIs and CBT in patients with anxiety and depression (Heresco-Levy et al., 2013). The compound's unique mechanism and tolerability profile support its further exploration in TRD populations.

7.3 Pioglitazone

Pioglitazone, a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist primarily used to treat type 2 diabetes, has demonstrated antidepressant properties, particularly in patients with metabolic disturbances (Lin et al., 2015).

Through its anti-inflammatory and insulin-sensitizing effects, pioglitazone may alleviate depressive symptoms by modulating neuroinflammation and oxidative stress. A small RCT revealed significant improvement in depressive scores among TRD patients treated with pioglitazone adjunctively compared to placebo (Lin et al., 2015). Its dual benefits in addressing both mood and metabolic dysfunctions render it a compelling candidate for further research.

7.4 Minocycline

Minocycline, a tetracycline antibiotic with neuroprotective and anti-inflammatory properties, has been repurposed for psychiatric indications. It modulates microglial activation and inhibits pro-inflammatory cytokines implicated in the pathophysiology of depression (Husain et al., 2020).

Preliminary clinical trials suggest that minocycline may be effective as an augmentation strategy in TRD. It has shown promising effects on mood, cognitive symptoms, and neuroinflammatory markers. However, these results are preliminary and larger, more robust trials are necessary (Husain et al., 2020).

7.5 N-Acetylcysteine (NAC)

NAC, a glutathione precursor and antioxidant, influences glutamatergic neurotransmission, oxidative stress, and inflammatory pathways. As such, it has emerged as a candidate adjunctive therapy in TRD (Russell et al., 2023).

Several studies have shown that NAC improves depressive symptoms, especially in patients with comorbid substance use or bipolar spectrum disorders. In a TRD context, NAC demonstrated modest but significant improvements in depression severity scales when added to conventional antidepressants (Russell et al., 2023). Its benign safety profile and affordability make it an attractive candidate.

7.6 Renin–Angiotensin System Modulators

The renin–angiotensin system (RAS), traditionally targeted in hypertension, has recently been implicated in mood regulation and neuroinflammation. Agents that block RAS components, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, show antidepressant-like effects in preclinical models and observational studies (Vian et al., 2017).

RAS modulators may exert mood-stabilizing effects by attenuating HPA axis hyperactivity and reducing oxidative stress and neuroinflammation. While no large-scale RCTs are available yet, observational data and mechanistic insights support further clinical investigation (Vian et al., 2017).

7.7 Celecoxib

Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, has been investigated as an adjunctive treatment in major depression due to its anti-inflammatory properties. A randomized, double-blind, placebo-controlled trial demonstrated that adjunctive celecoxib significantly enhanced fluoxetine's antidepressant effects over six weeks (Akhondzadeh et al., 2009).

The rationale lies in reducing pro-inflammatory cytokines implicated in depression pathogenesis. Celecoxib was well tolerated and may offer a rapid-onset effect. Anti- inflammatory augmentation strategies, such as celecoxib, represent a promising adjunctive approach, particularly for patients with elevated inflammatory markers (Akhondzadeh et al., 2009).

Drug/Class	MoA	Evidence	Status / Notes
Ketamine / Esketamine	Rapid NMDA antagonism → neuroplasticity	Strong evidence for rapid response/remission; modest augmentation effects; long-term data improving.	Expensive outpatient REMS; abuse and safety concerns; new combos in trials.
Psilocybin	5-HT1A agonist → neuroplasticity	Promising RCTs showing medium– large effects; breakthrough therapy; ongoing large trials.	Regulatory shift ahead; dosing, safety, long-term data still limited.
D-Cycloserine	NMDA glycine site modulator	Early trials show adjunct benefit in	Needs larger RCTs.
		TRD & bipolar; helps sustain ketamine effect.	
Minocycline	Anti-microglial/inflammatory	RCT in TRD showed large effect size (~0.98); safe.	Phase 2/3 confirmatory trials pending.
Celecoxib	COX-2 inhibitor → ↓PGE_2, cytokines	Small augmentation RCTs positive; no side effects.	Suitable for inflamed subtypes; needs larger replication.
N-Acetylcysteine	Antioxidant, anti-inflammatory	Meta-analysis shows benefit; qualitative improvements noted.	Good tolerability, awaiting high-powered trials.

Summary

Treatment-resistant depression (TRD) presents one of the most complex challenges in contemporary psychiatry. Affecting a substantial proportion of patients with major depressive disorder, TRD is associated with high morbidity, elevated suicide risk, and considerable socioeconomic burden. This work has comprehensively reviewed current and emerging therapeutic strategies aimed at managing this difficult-to-treat condition.

Initial chapters delineated the definition, epidemiology, and pathophysiological underpinnings of TRD, highlighting the limitations of traditional monoaminergic antidepressants and the urgent need for individualized, multi-modal approaches. Established augmentation strategies, such as dose optimization, switching antidepressants, and combining medications with psychotherapy, remain foundational but are often insufficient for many patients.

Electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) were examined as highly effective neuromodulatory treatments, particularly for patients with severe or life-threatening symptoms. These modalities, while underutilized due to stigma or accessibility issues, offer robust evidence-based alternatives when pharmacotherapy fails.

The introduction of rapid-acting agents such as ketamine and esketamine represents a paradigm shift in the treatment of TRD. These glutamatergic modulators, with their fast onset of action, address the urgent need for treatments that can alleviate suicidal ideation and severe symptoms more rapidly than conventional medications.

Similarly, the emerging evidence for psilocybin and psychedelic-assisted psychotherapy underscores the potential of integrative, experience-based interventions that act on both neurobiological and psychological levels. Though still experimental, these approaches may offer durable improvements with limited exposures.

Finally, the exploration of novel pharmacological candidates—such as lurasidone, minocycline, N-acetylcysteine, and anti-inflammatory agents like celecoxib—highlights the growing recognition of inflammation, oxidative stress, and neuroplasticity as central targets in TRD treatment. These agents, along with modulators of the renin–angiotensin system and metabolic pathways, signal a broadening of therapeutic horizons beyond neurotransmitter reuptake inhibition.

Taken together, the evolving landscape of TRD treatment demands a personalized, evidence- informed, and multidimensional strategy. Further high-quality research, especially head-to- head comparisons and long-term follow-ups, is essential to refine treatment algorithms and improve patient outcomes in this vulnerable population.

Data were obtained from: PubMed

Author Contributions:

-Conceptualization: Ignacy Rożek, Wojciech Gąska
-Methodology: Ignacy Rożek, Izabela Lekan
-Software: Ignacy Rożek, Joanna Mazurek
-Formal Analysis Ignacy Rożek, Agnieszka Brzezińska
-Investigation: Ignacy Rożek, Alicja Sodolska
-Resources Ignacy Rożek, Michał Lenart
-Data Curation: Ignacy Rożek, Barbara Madoń
-Writing Ignacy Rożek,
-Writing – Review & Editing: Wojciech Gąska, Barbara Teresińska
-Visualization: Ignacy Rożek, Wojciech Gąska
-Supervision: Wojciech Gąska

All authors read and approved the final manuscript.

Funding: This research received no external funding.

Ethical Assessment and Institutional Review Board Statement: Not applicable. As the article involves a review and synthesis of existing literature, rather than original research involving human subjects, ethical assessment and institutional review board statements are not applicable

Data availability statement: Not applicable

The authors declare no conflicts of interest.

Declaration of generative AI and AI-assisted technologies in the writing process: In preparing this work, the author used ChatGPT for the purpose of formatting, research and checking for errors. After using this tool/service, the author have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

REFERENCES

1. Kajumba, M. M., Kakooza-Mwesige, A., Nakasujja, N., et al. (2024). Treatment-resistant depression: Molecular mechanisms and management. Molecular Biomedicine, 5, 43. https://doi.org/10.1186/s43556-024-00205-y
2. Caldiroli, A., Capuzzi, E., Tagliabue, I., Capellazzi, M., Marcatili, M., Mucci, F., Colmegna, F., Clerici, M., Buoli, M., & Dakanalis, A. (2021). Augmentative pharmacological strategies in treatment-resistant major depression: A comprehensive review. International Journal of Molecular Sciences, 22(23), 13070. https://doi.org/10.3390/ijms222313070
3. Diaz, A. P., Fernandes, B. S., Quevedo, J., Sanches, M., & Soares, J. C. (2022). Treatment- resistant bipolar depression: Concepts and challenges for novel interventions. Brazilian Journal of Psychiatry, 44(2), 178–186. https://doi.org/10.1590/1516-4446-2020-1627
4. Steffens, D. C. (2024). Treatment-resistant depression in older adults. New England Journal of Medicine, 390(7), 630–639. https://doi.org/10.1056/NEJMcp2305428
5. Pandarakalam, J. P. (2018). Challenges of treatment-resistant depression. Psychiatria Danubina, 30(3), 273–284. https://doi.org/10.24869/psyd.2018.273

6. Zhdanava, M., Pilon, D., Ghelerter, I., et al. (2021). The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. Journal of Clinical Psychiatry, 82(2), 20m13699. https://doi.org/10.4088/JCP.20m13699
7. Naguy, A., Pridmore, S., Alhazeem, H., & Alamiri, B. (2023). Treatment-resistant juvenile depression—A quicksand? Psychopharmacology Bulletin, 53(4), 54–56. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10698857/
8. Nuñez, N. A., Joseph, B., Pahwa, M., et al. (2022). Augmentation strategies for treatment- resistant major depression: A systematic review and network meta-analysis. Journal of Affective Disorders, 302, 385–400. https://doi.org/10.1016/j.jad.2021.12.134
9. Moret, C. (2005). Combination/augmentation strategies for improving the treatment of depression. Neuropsychiatric Disease and Treatment, 1(4), 301–309. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2424118/
10. Cuomo, A., Beccarini Crescenzi, B., Bolognesi, S., et al. (2020). S-adenosylmethionine (SAMe) in major depressive disorder (MDD): A clinician-oriented systematic review. Annals of General Psychiatry, 19, 50. https://doi.org/10.1186/s12991-020-00298-z
11. Philip, N. S., Carpenter, L. L., Tyrka, A. R., & Price, L. H. (2010). Pharmacologic approaches to treatment-resistant depression: A re-examination for the modern era. Expert Opinion on Pharmacotherapy, 11(5), 709–722. https://doi.org/10.1517/14656561003614781
12. Gałecki, P., & Bliźniewska-Kowalska, K. (2021). Treatment-resistant depression – Recommendations of the National Consultant in the field of psychiatry. Psychiatria Polska, 55(1), 7–21. https://doi.org/10.12740/PP/OnlineFirst/115208
13. Hicks, P., Hicks, X. P., Meyer, H., & Shisslak, C. (2010). How best to manage treatment- resistant depression? The Journal of Family Practice, 59(9), 490–497. https://pubmed.ncbi.nlm.nih.gov/20824225/
14. Rush, A. J. (2023). Challenges of research on treatment-resistant depression: A clinician's
15. perspective. World Psychiatry, 22(3), 415–417. https://doi.org/10.1002/wps.21136
16. Karrouri, R., Hammani, Z., Benjelloun, R., & Otheman, Y. (2021). Major depressive disorder: Validated treatments and future challenges. World Journal of Clinical Cases, 9(31), 9350–9367. https://doi.org/10.12998/wjcc.v9.i31.9350
17. Kritzer, M. D., Peterchev, A. V., & Camprodon, J. A. (2023). Electroconvulsive therapy: Mechanisms of action, clinical considerations, and future directions. Harvard Review of Psychiatry, 31(3), 101–113. https://doi.org/10.1097/HRP.0000000000000365
18. Conelea, C. A., Philip, N. S., Yip, A. G., et al. (2017). Transcranial magnetic stimulation for treatment-resistant depression: Naturalistic treatment outcomes for younger versus older patients. Journal of Affective Disorders, 217, 42–47. https://doi.org/10.1016/j.jad.2017.03.063
19. Croarkin, P. E., Elmaadawi, A. Z., Aaronson, S. T., et al. (2021). Left prefrontal transcranial magnetic stimulation for treatment-resistant depression in adolescents: A double-blind, randomized, sham-controlled trial. Neuropsychopharmacology, 46(2), 462–469. https://doi.org/10.1038/s41386-020-00829-y
20. Kim, D. R., Wang, E., McGeehan, B., et al. (2019). Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder. Brain Stimulation, 12(1), 96–102. https://doi.org/10.1016/j.brs.2018.09.005
21. Yavi, M., Lee, H., Henter, I. D., Park, L. T., & Zarate, C. A. Jr. (2022). Ketamine treatment for depression: A review. Discover Mental Health, 2(1), 9. https://doi.org/10.1007/s44192- 022-00012-3
22. Nikolin, S., Rodgers, A., Schwaab, A., et al. (2023). Ketamine for the treatment of major depression: A systematic review and meta-analysis. EClinicalMedicine, 62, 102127. https://doi.org/10.1016/j.eclinm.2023.102127
23. Halpape, K., Pashovitz, R., Wanson, A., Hooper, M., & Peters, E. M. (2025). Intranasal racemic ketamine maintenance therapy for patients with treatment-resistant depression: A naturalistic feasibility study. BMC Psychiatry, 25(1), 23. https://doi.org/10.1186/s12888-024- 06448-x
24. Jagtiani, A. (2024). Novel treatments of depression: Bridging the gap in current therapeutic approaches. Exploration of Neuroscience, 3, 272–286. https://doi.org/10.37349/en.2024.00049
25. McIntyre, R. S., Rosenblat, J. D., Nemeroff, C. B., et al. (2021). Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: An international expert opinion on the available evidence and implementation. American Journal of Psychiatry, 178(5), 383–399. https://doi.org/10.1176/appi.ajp.2020.20081251
26. Vasiliu, O. (2023). Esketamine for treatment-resistant depression: A review of clinical evidence. Experimental and Therapeutic Medicine, 25(3), 111. https://doi.org/10.3892/etm.2023.11810
27. Esketamine hydrochloride for treatment-resistant depression. (2022). Australian Prescriber, 45(1), 27–28. https://doi.org/10.18773/austprescr.2021.061
28. Daly, E. J., Singh, J. B., Fedgchin, M., et al. (2018). Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: A randomized clinical trial. JAMA Psychiatry, 75(2), 139–148. https://doi.org/10.1001/jamapsychiatry.2017.3739
29. Jalloh, M. (2020). Esketamine (Spravato) for treatment-resistant depression. American Family Physician, 101(6), 339–340. https://pubmed.ncbi.nlm.nih.gov/32163257/

30. Borbély, É., Simon, M., Fuchs, E., Wiborg, O., Czéh, B., & Helyes, Z. (2022). Novel drug developmental strategies for treatment-resistant depression. British Journal of Pharmacology, 179(6), 1146–1186. https://doi.org/10.1111/bph.15753
31. Gałecki, P., Bliźniewska-Kowalska, K. M., Cubała, W. J., et al. (2024). Polish standard of treatment with racemic ketamine for patients with depressive disorders developed by a Working Group appointed by the National Consultant in the field of psychiatry. Psychiatria Polska, 58(3), 377–401. https://doi.org/10.12740/PP/189494
32. Carhart-Harris, R. L., Bolstridge, M., Day, C. M. J., et al. (2018). Psilocybin with psychological support for treatment-resistant depression: Six-month follow-up.
33. Psychopharmacology, 235(2), 399–408. https://doi.org/10.1007/s00213-017-4771-x
34. Dougherty, R. F., Clarke, P., Atli, M., et al. (2023). Psilocybin therapy for treatment resistant depression: Prediction of clinical outcome by natural language processing.
35. Psychopharmacology. https://doi.org/10.1007/s00213-023-06432-5
36. Borissova, A., & Rucker, J. J. (2024). The development of psilocybin therapy for treatment- resistant depression: An update. BJPsych Bulletin, 48(1), 38–44. https://doi.org/10.1192/bjb.2023.25
37. Agin-Liebes, G., & Davis, A. K. (2022). Psilocybin for the treatment of depression: A promising new pharmacotherapy approach. Current Topics in Behavioral Neurosciences, 56, 125–140. https://doi.org/10.1007/7854_2021_282
38. Carhart-Harris, R. L., Bolstridge, M., Rucker, J., et al. (2016). Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. The Lancet Psychiatry, 3(7), 619–627. https://doi.org/10.1016/S2215-0366(16)30065-7
39. Chiu, N. Y., & Chang, C. J. (2025). Efficacy and safety of adjunctive lurasidone in treatment resistant unipolar depression: An open-label single-arm pilot study. International Journal of Neuropsychopharmacology, 28(Suppl 1), i324–i325. https://doi.org/10.1093/ijnp/pyae059.578
40. Heresco-Levy, U., Gelfin, G., Bloch, B., et al. (2013). A randomized add-on trial of high- dose D-cycloserine for treatment-resistant depression. International Journal of Neuropsychopharmacology, 16(3), 501–506. https://doi.org/10.1017/S1461145712000910
41. Lin, K. W., Wroolie, T. E., Robakis, T., & Rasgon, N. L. (2015). Adjuvant pioglitazone for unremitted depression: Clinical correlates of treatment response. Psychiatry Research, 230(3), 846–852. https://doi.org/10.1016/j.psychres.2015.10.013
42. Husain, M. I., Cullen, C., Umer, M., et al. (2020). Minocycline as adjunctive treatment for treatment-resistant depression: Study protocol for a double blind, placebo-controlled, randomized trial (MINDEP2). BMC Psychiatry, 20(1), 173. https://doi.org/10.1186/s12888- 020-02553-9
43. Russell, S. E., Skvarc, D. R., Mohebbi, M., et al. (2023). The impact of N-acetylcysteine on major depression: Qualitative observation and mixed methods analysis of participant change during a 12-week randomised controlled trial. Clinical Psychopharmacology and Neuroscience, 21(2), 320–331. https://doi.org/10.9758/cpn.2023.21.2.320
44. Vian, J., Pereira, C., Chavarria, V., et al. (2017). The renin-angiotensin system: A possible new target for depression. BMC Medicine, 15, 144. https://doi.org/10.1186/s12916-017- 0916-3
45. Akhondzadeh, S., Jafari, S., Raisi, F., et al. (2009). Clinical trial of adjunctive celecoxib treatment in patients with major depression: A double-blind and placebo-controlled trial. Depression and Anxiety, 26(7), 607–611. https://doi.org/10.1002/da.20589