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REVIEW

Pharmacological treatment of treatment-resistant depression: towards evidence-based recommendations

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Summary

Depression, a major global public health concern and leading cause of disability, necessitates effective management. This paper, as part of the development of comprehensive guidelines for the treatment of depressive disorder in Serbia, delves into the pharmacological treatment of treatment-resistant depression (TRD), focusing on augmentative and switching strategies, aiming to address the lack of response to standard treatments. The focus is on the efficacy and tolerability of various pharmacological agents, aimed at facilitating informed clinical decisions. In TRD, augmentation strategies involving atypical antipsychotics, NMDA antagonists, mood stabilizers, and other compounds are examined. Finally, the importance of an individualized approach in deciding between augmentation and switching strategies is emphasized. This narrative review aims to inform treatment guidelines and encourages a collaborative approach, which considers individual patient factors, to improve the quality of care for individuals with treatment-resistant depression.

Keywords: treatment-resistant depression, pharmacological treatment, guidelines

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INTRODUCTION

Depression, a leading cause of disability worldwide, presents a significant public health concern and has been the topic of recent investigations in Serbia (1). The effective management of this condition is paramount, and it requires a comprehensive understanding of the various treatment modalities available (2). This paper serves as a preparatory work for the development of comprehensive guidelines on the treatment of depressive disorders. These guidelines are being developed under the auspices of the Advisory Board on Mental Health of the Republic of Serbia.

Our aim is to provide a narrative review of the current literature on the pharmacological treatment of treatment-resistant depression (TRD). This work is intended to inform the development of evidence-based guidelines that will aid clinicians in making informed decisions about treatment options. This challenging condition, marked by a lack of response to standard treatments, necessitates a deeper understanding of alternative pharmacological strategies. We aim to provide a comprehensive narrative review of the current pharmacological options for managing TRD, drawing from the latest research and clinical guidelines. Brain stimulation strategies, in particular electro-convulsive therapy, has a strong evidence base as a treatment option for this condition, but lacks consistent guidelines (3)". However, it is important to note that our focus will remain on pharmacological interventions and will not include discussions on psychotherapeutic, brain stimulation, or other non-pharmacological interventions.

Our preparatory work is grounded in a thorough analysis of several authoritative sources in the field of psychiatry and mental health. These include the 14th edition of the Maudsley Prescribing Guidelines in Psychiatry (4), the American Psychiatric Association Practice Guidelines (APA) (5), the World Federation of Societies of Biological Psychiatry Guidelines (WFSBP) (6), and the Canadian Network for Mood and Anxiety Treatments Clinical Guidelines (CANMAT) (7). We also referred to the National Institute for Health and Care Excellence Guidelines (NICE) (8) for the treatment of depressive disorders in adults, as well as the recommendations of the Slovenian Medical Association (9). These comprehensive and well-respected resources have served as the foundation for the development of our recommendations, providing a robust basis for our analysis and subsequent guideline development. In addition, individual meta-analyses and RCTs were analyzed.

While we discuss various treatment strategies and their potential benefits and drawbacks, our aim is not to issue definitive recommendations. Instead, our goal is to inform and contribute to the ongoing dialogue on this topic. We encourage clinicians and policymakers to consider this information in conjunction with their professional judgment, patient preferences, and local regulations and practices when making treatment decisions. We also advocate for further research and guideline development by official health authorities to ensure the most effective and appropriate care for individuals with TRD. By providing a narrative review of the current evidence, we aim to facilitate the development of robust, evidence-based guidelines that will ultimately improve patient outcomes.

LACK OF THERAPEUTIC RESPONSE AND TREATMENT-RESISTANT DEPRESSION

Estimates suggest that 53% of patients with major depressive disorder, when treated with standard first-line psychopharmacological medications, fail to achieve remission. Moreover, 67% do not attain a satisfactory therapeutic outcome (10). Even with the implementation of a stepwise approach—where different antidepressants are sequentially employed—up to 20% of patients continue to experience significant symptoms beyond a two-year period (11).

Non-responsiveness to first-line pharmacotherapy is linked with numerous adverse outcomes. These include a decreased quality of life, an increased lifetime hospitalization rate, greater usage of emergency medical services, a higher risk of unemployment, and diminished productivity at work, relative to those who respond favorably to treatment (12).

Given the aforementioned factors, the concept of TRD, also known as refractory depression or "difficult-to-treat depression", was introduced (12). Various models have been proposed to quantify the lack of therapeutic response, but a definitive consensus on the precise definition of TRD remains elusive in literature. The most widely accepted definition of TRD encompasses the failure to respond therapeutically to two consecutive, adequate treatments using different antidepressants during a single depressive episode. However, there remains contention about what characterizes an adequate treatment, specifically, no well-defined criterion exists for sufficiently long treatment durations or adequately high doses of the recommended antidepressants (11,13). Moreover, ongoing discussions continue to debate whether TRD refers to a lack of a therapeutic response to any two antidepressants, or whether it specifies the absence of a response to two antidepressants from different classes, such as SSRIs and NaSSAs (14).

Current evidence suggests that an early improvement, defined as a minimum 20% symptom reduction after 2-4 weeks of treatment, is linked with the emergence of a therapeutic response and remission after 6-12 weeks of treatment (15). Conversely, the absence of early improvement after 2-4 weeks tends to predict a later lack of therapeutic response or remission. However, the literature lacks reliable evidence supporting the benefits of an early substitution of the initially prescribed antidepressant

(14). Consequently, it is suggested that for patients who do not demonstrate early improvement after 2-4 weeks, the antidepressant dosage should be increased in line with the therapeutic range and the patient's tolerance and the occurrence of side effects (7).

Pseudo-resistant depression

A considerable number of patients who fail to exhibit a therapeutic response may have "pseudo-resistant" depression, which does not equate to TRD. Pseudo-resistance primarily implies an inaccurate diagnosis of major depressive disorder. Often, these cases are instances of bipolar depression, where a lack of therapeutic response is anticipated given the divergent treatment approach compared to unipolar depressive disorder. Differentiating between bipolar and unipolar depression is sometimes very difficult in absence of indubitable signs of hypomania (16). In such cases, retracing of the steps to the history taking along with using particular approaches such as phenomenologically based interviews and assessments is recommended (17–19)

Pseudo-resistant cases also include instances where suboptimal antidepressant therapy doses have been prescribed, where the duration of the therapy was insufficient, or where treatment was discontinued due to poor tolerance of side effects, inadequate compliance, or any other reason (11,20). Notably, even when dosed according to guidelines, antidepressant treatment may not achieve therapeutic concentrations in the blood. Some patients are considered rapid metabolizers, which can lead to psychotropic active ingredients being eliminated and achieving lower blood levels than typical for the general population due to genotypic differences associated with the cytochrome P450 system (21). Additionally, from a pharmacokinetic perspective, careful documentation of a patient's concurrent, non-psychiatric therapy is essential due to potential drug-drug interactions.

While a diagnosis of major depressive disorder usually excludes organic causes in its etiology, a lack of therapeutic response demands a re-evaluation of the diagnosis. This is particularly important in the light of physical conditions stemming from endocrine origins (such as hypothyroidism or Cushing's syndrome), neurological conditions (of both cortical and subcortical origins), neoplastic diseases (like pancreatic cancer), autoimmune disorders (including systemic lupus erythematosus and overlap syndrome), vitamin deficiencies, and specific viral infections (22).

PHARMACOLOGICAL APPROACHES TO TREATMENT-RESISTANT DEPRESSION

Pharmacological approaches to TRD encompass: (1) switching or optimizing antidepressant dose, (2) augmentation strategies.

(1) Switching or optimizing antidepressant dose

Evidence suggests that changing antidepressants in individuals lacking a therapeutic response constitutes a viable therapeutic strategy. Although some opinions suggest the subsequent antidepressant should have a different mechanism of action, several randomized controlled trials and meta-analyses have found no significant differences with regards to improvement in efficacy when changing an antidepressant within a group (e.g., replacing one SSRI with another), compared to an antidepressant from another group (i.e., with a different mechanism of action, e.g., replacing an SSRI with bupropion) (23). On the other hand, one meta-analysis indicated a benefit when substituting an SSRI antidepressant with another class antidepressant (bupropion, mirtazapine, and venlafaxine), potentially providing an efficiency gain in the therapeutic response (28% non-SSRI versus 23.5% SSRI). Despite the current lack of consensus on this matter in literature, it is essential to note that individual differences in efficacy within SSRI antidepressants, albeit small, do exist (24). In line with this, after non-response, using a more effective medication when switching is advised.

(2) Augmentation

Augmentation refers to the addition of a new medication to the existing antidepressant therapy that did not yield a satisfactory therapeutic response (11). The results of randomized controlled studies, as well as a variety of international guidelines suggest that effective augmentation strategies can include atypical antipsychotics, NMDA antagonists, mood stabilizers, antidepressants, and other compounds.

Atypical antipsychotics

Given that atypical antipsychotics are drugs that exert their effects through activity on a wide range of receptors, including serotonergic receptors, a large number of randomized controlled trials have been conducted in recent years using these drugs as augmentation therapy in cases of inadequate response to first-line antidepressants, most commonly SSRI/SNRI.

Aripiprazole. Among atypical antipsychotics, aripiprazole is one of the most studied in TRD. Its effectiveness in TRD is thought to be based on its activity as a partial antagonist for various serotonin receptors (5-HT1A, 5-HT2A, 5-HT2B, 5-HT6, and 5-HT7) (25). Even using a rigorous and commonly used clinical definition of TRD (absence of therapeutic response to two adequate doses of applied antidepressants for long enough), results from four randomized controlled studies have so far shown that aripiprazole represents an effective augmentation strategy (26). Furthermore, one randomized controlled study found that the use of aripiprazole at lower doses did not increase the level of side effects compared to placebo (27).

Quetiapine. Sharing structural similarities with clozapine, quetiapine, a second-generation antipsychotic, exhibits differing receptor activity properties based on dosage. At the 50 mg dosage level, quetiapine primarily serves as an H1 receptor antagonist, inducing notable sedative effects. When the dosage is increased to 300 mg, quetiapine inhibits the 5-HT2C receptor and the norepinephrine transporter (NET). This particular characteristic is believed to underpin its antidepressant capabilities. With even higher dosages (800 mg), quetiapine blocks over 60% of D2 receptors, providing it with an antipsychotic action (28). Quetiapine's effectiveness as an augmentation strategy in TRD has received validation from several randomized controlled trials (28). One of these studies demonstrated that quetiapine outperformed lithium, a treatment historically recommended as the first line of augmentation in TRD (29). Quetiapine was notably effective in alleviating anxiety symptoms in patients with depression (30). As a result, the utilization of quetiapine as an augmentation strategy for individuals with TRD is particularly advisable, especially when patients exhibit persistent anxiety and symptoms of insomnia (28).

Risperidone. In addition to antagonizing D2 receptors, risperidone is also an antagonist of 5-HT2 receptors. Studies in TRD have shown that risperidone reduces depressive symptoms compared to placebo. However, despite the considerable effect sizes, risperidone has not undergone the same level of scrutiny in randomized controlled trials as compared to quetiapine and aripiprazole. Moreover, it is believed to be less well-tolerated than these aforementioned medications, particularly due to the more common incidence of hyperprolactinemia (28).

Olanzapine. Olanzapine is an atypical antipsychotic that has greater activity on 5-HT2A receptors than on D2 receptors in terms of antagonism. Additionally, olanzapine is an antagonist of 5-HT2C receptors, which is why it is thought to affect affective symptoms in some patients (28). To date, two randomized controlled studies have examined and demonstrated the efficacy of olanzapine as an augmentation strategy in cases of therapeutic non-response in depressive disorder. Compared to aripiprazole, quetiapine, and risperidone, the efficacy of olanzapine as an augmentation strategy in TRD is the lowest, according to the current evidence" (26). Also, as with risperidone, poor tolerance of olanzapine has been demonstrated, in terms of a higher burden of side effects, primarily in the form of metabolic disorders (31). On the other hand, it has been shown that the specific combination of olanzapine/fluoxetine has significant efficacy in TRD and may potentially bring more benefits than augmenting other SSRI/SNRI psychotropics with olanzapine (32).

Brexpiprazole. A third-generation antipsychotic, the most recently developed, brexpiprazole, achieves its effect through partial agonism of D2 receptors. Several studies have shown its effectiveness compared to placebo in patients with a lack of therapeutic response (33,34). However, considering the relatively recent appearance of this drug, and the smaller number of meta-analyses that included this drug in the analysis (26,35), its advantage over existing antipsychotics as augmentation agents has not been fully clarified yet. There is some evidence for a variety of other atypical antipsychotics in depression, such as cariprazine, but much of it is based on case reports (36), or either low quality or insufficiently rigorous research.

NMDA antagonists

Recent studies of new psychopharmaceutical agents have begun investigating drugs that function through full or partial antagonism of NMDA receptors, which are found on GABA-ergic interneurons that modulate glutamatergic transmission. The antagonism of NMDA receptors is hypothesized to activate various signaling pathways, leading to increased local protein synthesis, which in turn enhances the surface area of dendritic spines and improves the impaired synaptic activity of neurons in depression (37). This category of drugs includes D-cycloserine, minocycline, and ketamine. Given their experimental status and a lack of widespread use in clinical practice, D-cycloserine and minocycline are not evaluated in this paper.

Ketamine. Several meta-analytic studies examining TRD augmentation strategies have found ketamine to be effective (26,35). A recent meta-analysis indirectly comparing TRD augmentation agents, including atypical antipsychotics, mood stabilizers, and NMDA antagonists, suggests that the most likely positive outcome is achieved by augmenting the initial antidepressant with NMDA antagonists (35). Using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework, it was shown that NMDA antagonists as augmentation agents for TRD currently hold a high level of evidence (35). However, given the relatively short period of ketamine's clinical use, its side effects may be underestimated, and its tolerability overestimated, particularly during repeated administration (38). It is important to note that there are different formulations of ketamine. Intravenous infusion of ketamine (0.5 mg/kg over 40 minutes) is considered the gold standard, but the efficacy of intranasal spray has been confirmed in multiple randomized controlled studies (39,40). Recently, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved esketamine nasal spray for TRD in adults (41). Compared to other augmenting agents like atypical antipsychotics or mood stabilizers, esketamine offers a different mechanism of action, as well as rapid onset effects, and may be particularly useful in cases where these traditional augmenting agents have failed or are not suitable (42). Nevertheless, the clinical decision to use esketamine must weigh its rapid onset of action against factors like its side effect profile, the need for clinical supervision during adminis-

tration, and concerns about long-term safety and potential for abuse (43). Moreover, the cost and accessibility of esketamine may also influence its use in clinical practice, particularly when compared to other more established and possibly less expensive augmenting agents (44).

Mood stabilizers

Lithium. Efficacy of lithium as an augmenting agent for major depressive disorder was established in older studies, often in combination with Tricyclic Antidepressants (TCAs) (11,45). Randomized controlled trials that implemented lithium augmentation of SSRI demonstrated this strategy's effectiveness, albeit with a wide confidence interval (7,46). Recent meta-analyses, adhering to the conventional clinical definition of TRD, indicate that lithium continues to be a reliably effective augmentation strategy for these patients (26,35). When augmenting antidepressant therapy with lithium, it's crucial to establish a dosing regimen achieving blood levels of at least 0.4 mmol/l (47).

Lamotrigine. Meta-analytical study findings indicate that lamotrigine, as a SSRI therapy augmenter, is effective and well-tolerated (48,49). The negative aspects of employing lamotrigine as an augmentation strategy include the necessity for slow titration and uncertainties regarding the dosing regimen (4).

Even though there have been some investigations into the use of carbamazepine and valproate as augmenting agents for TRD, rigorous research yielding high-quality evidence supporting their efficacy remains notably scarce. Notably, some data indicate that valproate produces antidepressant-like effects in animal models (50). Also, while some open-label (51) and pilot studies (52) demonstrated efficacy in TRD, the availability of robust data, to the best of our knowledge, remains insufficient. In the case of carbamazepine, one study showed no gain in efficacy after augmentation of mirtazapine (53). In line with this, authoritative resources such as Maudsley Prescriber Guidelines 14th edition, as well as most recent guidelines on approaches to TRD do not endorse the use valproate or carbamazepine in TRD (4,9).

Antidepressants

Mirtazapine. Mirtazapine is a well-established antidepressant that has proven effective as a first-line treatment for depressive disorders when used in monotherapy. Two meta-analytic studies that included a significant number of randomized controlled trials examining the use of mirtazapine as an augmentation agent for TRD suggested that this drug might be effective when used in combination with SSRI and SNRI therapy (54,55). However, a recent high-quality randomized controlled trial did not demonstrate the efficacy of mirtazapine for this particular indication (56).

Bupropion. The results of the STAR*D study showed that bupropion was an effective augmentation strategy for those who did not respond to the administration of citalopram (57). Its efficacy in TRD was later confirmed through randomized controlled trials and one meta-analysis (54). A particular advantage of augmenting SSRI/SNRI therapy with bupropion is the potential to reduce sexual side effects, which are very common during monotherapy with SSRIs/SNRIs (4). The summary of augmentation strategies in TRD is presented in **Table 1**.

Table 1. Summary of pharmaceuticals with significant evidence base effective for augmentation of treatment-resistant depression.

Augmenting agent	Dose range
Aripiprazole	2.5 – 15 mg
Quetiapine	150 – 300 mg
Risperidone	1 – 3 mg
Olanzapine	2.5 – 10 mg
Brexipiprazole	1 – 3 mg
Esketamine (intranasal)	28 – 84 mg
Ketamine (intravenous)	0.5 mg/ kg over 40 min.
Lithium	600 – 800 mg; 0.4 – 0.8 mmol/l serum level
Lamotrigine	100 – 200 mg
Mirtazapine	30 – 60 mg
Bupropion	150 – 300 mg

*Dosage ranges are presented based on evidence from randomized controlled trials and authoritative international guidelines referenced throughout the text

Augmentation or antidepressant switch?

As there are no clear indicators of using either augmentation or switching as a better strategy, several factors can influence this decision (7). Most importantly, the final decision should be tailored to each individual patient's characteristics. In general, it is recommended to consider switching antidepressant medication in the following cases: (a) when there is a lack of therapeutic response (less than 25% improvement) to the initial antidepressant; (b) when the patient experiences poor tolerability due to adverse effects of the first antidepressant; (c) when it is feasible to wait for a longer period for a therapeutic response (in cases of less functional impairment); and (d) when the patient expresses a preference to switch to a different antidepressant. On the other hand, augmentation is recommended in the following situations: (a) when there is an inadequate therapeutic response to two or more antidepressants; (b) when the first antidepressant is well-tolerated in terms of side effects; (c) when there is a partial therapeutic response to the first antidepressant (more than 25% but less than 50% improvement); (d) when residual symptoms persist after treatment with the first antidepressant, or when specific adverse effects can be targeted with augmentation agents; (e) when waiting for a therapeutic response is not feasible due to significant functional impairment; and (f) when the patient prefers adding psychopharmacological agents to the existing antidepressant treatment.

Polypharmacy should be approached with caution due to its potential to increase the risk of adverse effects and reduce treatment tolerability. While the analysis of literature provides valuable insights into the efficacy and tolerability of specific augmentation strategies, it is important to acknowledge that the individualized treatment plan for each patient should be developed through collaborative decision-making. It is crucial to consider individual patient factors that contribute to the therapeutic approach, as the therapeutic approach cannot be rigidly standardized.

CONCLUSION

In summary, we present a detailed narrative review of pharmacological approaches to TRD, with the goal of contributing to evidence-based clinical guidelines in Serbia. Our comprehensive analysis spans various therapeutic strategies for TRD, underlining the importance of tailoring treatments to individual patient profiles, which includes giving special attention to factors like the severity of depression and any coexisting conditions. Although our focus is on pharmacological interventions, we recognize the role of non-pharmacological methods, such as psychotherapy and brain stimulation, which are not covered in this narrative review. It is essential for clinicians and policymakers to integrate this knowledge with their professional expertise, taking into account patient preferences and the specific healthcare context of Serbia.

Author contributions

SJ and MI conceived of the work. SJ drafted the manuscript, synthetized the literature and critically revised the work. MI provided expertise in the interpretation of the data and critically revised the work. Both authors approved the final manuscript.

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FARMAKOLOŠKI TRETMAN TERAPO-REZISTENTNE DEPRESIJE: KA PREPORUKAMA ZASNOVANIM NA DOKAZIMA

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Sažetak

Depresija je jedan od vodećih uzroka invaliditeta i značajan javno-zdravstveni izazov, usled čega zahteva efikasan tretman. Ovaj rad predstavlja pregled farmakološkog tretmana i deo je izrade sveobuhvatnih smernica za lečenje depresivnog poremećaja. U ovom radu izložene su strategije za lečenje terapo-rezistentne depresije (TRD) koju karakteriše odsustvo odgovora na uobičajen tretman. Naglasak je na efikasnosti i podnošljivosti različitih antidepresiva, sa ciljem olakšavanja donošenja kliničkih odluka na osnovu dosadašnjih dokaza iz literature. Lečenje TRD može podrazumevati strategije augmentacije, ili zamene antidepresiva. U domenu strategija augmentacije, razmotrena je primena atipičnih antipsihotika, NMDA antagonista, stabilizatora raspoloženja i drugih biološki aktivnih jedinjenja. Odluka o izboru između različitih strategija augmentacije ili zamena antidepresiva temelji se na individualnim faktorima pacijenta. Ovaj sveobuhvatni pregledni rad teži da doprinese formiranju smernica za lečenje TRD, promovišući pristup saradnje i zajedničkog donošenja odluka između pacijenta i kliničara, uzimajući u obzir individualne specifičnosti pacijenta, radi poboljšanja nege osoba sa TRD.

Ključne reči: terapo-rezistentna depresija, farmakološki tretman, smernice

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