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Major Depressive Disorder as a Condition Negatively Impacting Both Mental and Physical Functioning. What to Do When There Is a Treatment Resistance?

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ABSTRACT

The objective of this article is to assess the efficacy and safety of diverse therapeutic strategies for treatment-resistant depression (TRD), encompassing both pharmacological and non-pharmacological interventions. Additionally, the review identifies potential avenues for future research within this domain.

The article compares the results of selected studies. We conducted a literature search in November of 2024, using PubMed. Six studies were identified, chosen, and appraised. Among these studies, three are systematic reviews and three are narrative literature reviews.

If it comes to treatment efficacy studies have demonstrated the effectiveness of several strategies. Ketamine and esketamine have shown rapid and substantial efficacy in mitigating the symptoms of TRD. Augmentation with aripiprazole and quetiapine has also been found to enhance the response to antidepressant treatment. The combination of olanzapine and fluoxetine is effective for treating TRD, however, it may be associated with metabolic side effects. Augmentation with lithium, triiodothyronine (T3), and lamotrigine shows promising results, though further research is required to fully evaluate their efficacy and safety in TRD management.

The management of TRD is associated with several challenges. These include the absence of a standardized definition and grading system, which impedes the comparison of research outcomes. The multifactorial nature of TRD further complicates the development of a universal treatment strategy. Summarizing, there are several treatment strategies available for TRD, however, the most effective approach should be personalized for each patient. Ongoing research is critical to advancing our understanding of TRD and developing more effective therapeutic options.
Keywords: depression, treatment-resistant depression, major depressive disorder, mood disorder, antidepresant, augmentation, electroconvulsive stimulation, novel therapies

Introduction:

Major Depressive Disorder (MDD) and related mood disorder syndromes are among the most common psychiatric disorders encountered in both specialized and general medical practice (Voineskos et al., 2020). The prevalence of individuals diagnosed with major depressive disorder is steadily increasing. Recurrent depressive disorder (MDD) causes significant impairments in occupational and social functioning, contributing to substantial global economic burdens (Caldiroli et al., 2021; Cui et al., 2024). Depressive symptoms have a significant impact on sleep quality and physical activity levels, which in turn affects overall physical fitness. Conversely, regular physical activity can contribute to improvements in mental health, leading to a reduction in symptoms of depression and anxiety, an increase in self-esteem, and overall well-being, which often results in improved sleep quality. The interrelationship between these factors is clearly evident. (Griffiths et al., 2022) It is estimated that as many as one in five adults in the United States meets the diagnostic criteria for Major Depressive Disorder (MDD) at some point in their lifetime (Ruberto et al., 2020). Mood disorders manifest at various stages of life, presenting diverse combinations of symptoms. While depressive symptoms may occasionally occur as part of normal human experiences, Major Depressive Disorder (MDD) can be debilitating, and in the most severe cases, life-threatening.

MDD can occur at any age, and variations in biological susceptibility, age of onset, risk factors, clinical presentation, and comorbidities are characteristic of patients with this diagnosis. Consequently, MDD is a highly heterogeneous disorder (Voineskos et al., 2020). Nearly one-

third of patients diagnosed with a major depressive episode do not achieve remission following two or more trials of first-line antidepressant therapies, thereby meeting the criteria for treatment-resistant depression (TRD). Furthermore, nearly half of patients who show improvement in depressive symptoms continue to experience residual symptoms. The presence of these symptoms adversely affects their functional capacity and increases the likelihood of relapse into a severe episode of the disorder. (Touloumis 2021) As the likelihood of remission diminishes with each subsequent pharmacological intervention, it is essential for clinicians to thoroughly understand the characteristics and risk factors associated with TRD, identify subtypes of major depressive disorder that demonstrate reduced responsiveness to standard treatments, and be well-informed about available therapeutic alternatives. (Kverno et al., 2021) In the context of predictive factors for treatment-resistant depression (TRD), the most frequently identified were high symptom severity (9 studies), the presence of suicidal thoughts (8 studies), and recurrent depression (6 studies). Among the primary physical risk factors, cardiovascular conditions (4 studies), pain (3 studies), and thyroid disorders (3 studies) were most commonly noted. Regarding demographic factors, younger age (7 studies) and female gender (6 studies) were identified as significant predictors of treatment resistance in depression. (O'Connor et al., 2023) Despite the absence of a universally accepted definition of Treatment-Resistant Depression (TRD), the lack of response to at least one adequate trial of antidepressant therapy is considered an unfavorable prognostic indicator (Ruberto et al., 2020). There is still no widespread consensus on the definition of TRD. Patients with treatment-resistant depression (TRD), according to the guidelines of the European Medicines Agency (EMA), are defined as individuals who do not experience noticeable clinical improvement after treatment with at least two antidepressants from different pharmacological classes, administered at adequate doses for a sufficiently long period, in adherence to therapeutic recommendations. This definition aligns with the guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) for unipolar depressive disorder (Caldiroli et al., 2021).

Treatment-resistant depression (TRD) may lead to prolonged and costly hospitalizations and poses specific challenges regarding therapeutic strategies and effective treatment methods. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the cumulative remission rate during treatment with up to four consecutive pharmacological interventions over 14 months was analyzed. Results indicated that 67% of patients achieved remission. Nevertheless, in 10–20% of individuals with unipolar major depression (MDD), significant symptoms persisted for two years or longer despite multiple treatment attempts. Although

antidepressants are considered effective in treating MDD, they fail to achieve remission in approximately one-third of patients (Voineskos et al., 2020).

Several models for classifying resistance to depression treatment (TRD) have been proposed in the literature. The first model, developed by Thase and Rush, defines levels of resistance ranging from the failure of a single antidepressant trial to the lack of response to electroconvulsive therapy (ECT). Alternative approaches, such as the Massachusetts General Hospital (MGH) staging method, focus on documenting dose optimization of pharmacotherapy and the number of unsuccessful interventions. Souery's operational criteria characterize TRD as the lack of efficacy of a single antidepressant trial conducted at an appropriate dose for 6–8 weeks. Conversely, the Maudsley Staging Method (MSM) incorporates a multidimensional approach to assess the degree of resistance. Most TRD studies adopt a definition requiring at least two adequately conducted antidepressant treatment trials without achieving satisfactory therapeutic response, though the notion of a "satisfactory response" remains subject to debate (Voineskos et al., 2020).

Diagnosing Treatment-Resistant Depression (TRD) can be complicated by the phenomenon of "pseudoresistance." This occurs in cases where patients received suboptimal doses of antidepressants or prematurely discontinued therapy due to adverse effects, nonadherence, or improper dosing. Additionally, comorbid disorders, such as anxiety disorders, personality disorders, or substance use disorders, can create a complex clinical picture that complicates the evaluation of treatment efficacy. Assessing patients for TRD is further challenged by the risk of inaccuracies in reconstructing the course of prior pharmacotherapy trials and therapeutic responses. Standardized diagnostic tools, such as the Hamilton Depression Rating Scale (HDRS) or the Inventory of Depressive Symptoms (IDS), as well as systematic documentation of treatment history using instruments like the Antidepressant Treatment History Form (ATHF), may enhance the objectivity of this evaluation (Voineskos et al., 2020).

Treatment of TRD: In cases of inadequate response to antidepressant therapy, available strategies include optimizing the dosage of the current medication, switching to another antidepressant from a different class, combination therapy using two antidepressants, or augmentation with a non-antidepressant agent. Each of these approaches has specific advantages and limitations. Combination therapy or augmentation allows for leveraging the partial therapeutic response achieved with the initial treatment, which may increase the likelihood of remission. However, the addition of another medication may pose a higher risk of adverse effects. Alternatively, switching to a different antidepressant may potentially reduce the severity of side effects but carries the risk of losing previously achieved partial improvement

and the possibility of withdrawal symptoms, especially if discontinuation occurs too quickly (Ruberto et al., 2020). Guidelines for the treatment of treatment-resistant depression (TRD) are not fully in line with the principles of evidence-based medicine, and current treatment methods are largely empirical. Therefore, higher-quality research is necessary to improve clinical practice and facilitate the selection of therapeutic pathways. (Pandarakalam, 2018)

According to guidelines developed by the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the American Psychiatric Association (APA), atypical antipsychotics (AAs) are recognized as an effective augmentation option in antidepressant therapy. Additionally, studies have evaluated the efficacy of other strategies, such as using mood stabilizers, combinations of antidepressants, stimulants, thyroid hormones, and ketamine (Gelenberg et al., 2010; Kennedy et al., 2016). Meta-analyses have confirmed the efficacy of augmentation with AAs, lithium, ketamine, and esketamine in the treatment of treatment-resistant depression (Carter et al., 2020; Strawbridge et al., 2019; Vázquez et al., 2021; Zhou et al., 2015) (Nuñez et al., 2022). This review aims to support clinicians in making informed decisions regarding the selection of the most appropriate pharmacological interventions within the complexity of TRD treatment.

Table 1: Augmentation Agents used for TRD pharmacotherapy

Pharmacological class	**Substance**	**Considered dose of medication**
SGA	Aripiprazole	2-20mg/d
SGA	Brexpiprazole	1-3mg/d
SGA	Quetiapine	max 600mg/d
SGA	Olanzapine	12,5-13,5mg/d
SGA	Risperidone	1-2mg/d
SGA	Ziprasidone	average approx. 82mg/d
Mood Stabilizers	Lithium	no exact data
Mood Stabilizers	Lamotrigine	max 200mg/d
Thyroid Hormones	Liothyronine (L3)	average approx. 37,5mcg/d
Thyroid Hormones	Levothyroxine (L4)	150-300mcg/d
Dopaminergic Agents	Modafinil	average approx. 249mg/d
Dopaminergic Agents	Lisdexamfetamine	43,5-46,5mg/d
NaSSA	Mirtazapine	average approx. 30mg/d
TCA	Nortryptyline	no exact data

Other	Buspirone	20-50 mg/d
Dissociative anesthetics	Ketamine	0,1-1,0mg/kg iv.
Dissociative anesthetics	Esketamine	14mg 1x/ 2 weeks – 84mg 2x/ 1week

Information in the table above was taken from sources (Nuñez et al., 2022; Caldiroli et al., 2021; Borbély et al., 2022; Ruberto et al., 2020)

Materials and methods:

The search for relevant articles was conducted in November 2024 using the PubMed database. To identify potentially eligible studies, a controlled vocabulary was used, complemented by keywords such as ”treatment-resistant depression”, „major depressive disorder”, „affective disorders”, „augmentation treatments”, „antidepressants” and „novel therapies”. The search was limited to publications in English. The selection process focused on meta-analyses, systematic reviews, and narrative literature reviews published within the past five years. Studies centered on animal models of the subject were excluded from consideration. Ultimately, six scientific studies were included in the analysis: „Augmentation strategies for treatment-resistant major depression”, „A systematic review and network meta-analysis”, „Augmentative Pharmacological Strategies in Treatment-Resistant Major Depression: A Comprehensive Review”, „Electroconvulsive Therapy: Mechanisms of Action, Clinical Considerations, and Future Directions”, „Management of Treatment-Resistant Depression: Challenges and Strategies”, „Novel Drug Developmental Strategies for Treatment-Resistant Depression” and „Pharmacological Treatments for Patients with Treatment-Resistant Depression”. These articles were read in full.

The article ”Augmentation strategies for treatment-resistant major depression: A systematic review and network meta-analysis” analyzed data from 65 RCTs encompassing 19 different adjunctive medications, including stimulants, atypical antipsychotics, thyroid hormones, antidepressants, and mood stabilizers. The analysis focused on treatment response rates, remission rates, and cases of drug discontinuation for any reason. The statistical methods used in the network meta-analysis allowed for comparisons across all 19 drugs, even when they were not directly compared in individual studies. The authors employed a random-effects model to account for variability between studies and conducted heterogeneity and inconsistency tests to assess whether the differences between studies were statistically significant. The primary outcome was response rates [(defined as a decrease of ≥ 50% of the validated behavioral scales for depression (e.g. HAMD or MADRS)]. Secondary outcomes included: remission rates,

defined as a score below <10 for the MADRS or <7 on the HAMD or as per the study, and all cause discontinuation rates calculated for the patients who discontinued the trial. (Nuñez et al., 2022)

”Augmentative Pharmacological Strategies in Treatment-Resistant Major Depression: A Comprehensive Review” is a study that analyzed 107 scientific articles meeting the inclusion criteria. The studies were selected from major psychiatric databases, including PubMed, ISI Web of Knowledge, and PsychInfo.

„Electroconvulsive Therapy: Mechanisms of Action, Clinical Considerations, and Future Directions” is a narrative literature review. Instead of conducting a systematic review with predefined inclusion criteria and statistical analysis, the authors curated and analyzed key studies and findings. The review focuses on the efficacy of electroconvulsive therapy, its mechanisms of action, and critical clinical considerations, including the optimization of stimulation parameters, electrode placement, adjunctive pharmacological support, and patient selection.

„Management of Treatment-Resistant Depression: Challenges and Strategies” is classified as a narrative literature review. The review adopts a descriptive and synthetic approach. Articles included in the study were retrieved from the PubMed database; however, the authors do not specify selection criteria or provide information on the number of publications ultimately included. The review discusses various approaches to managing treatment-resistant depression, including traditional and novel pharmacological strategies, psychotherapy, and different forms of brain stimulation (Electroconvulsive Therapy, Repetitive Transcranial Magnetic Stimulation, Conventional High Frequency Left DLPFC rTMS, Deep rTMS, Theta-Burst Stimulation, Accelerated rTMS Protocols, Accelerated rTMS Protocols, Deep Brain Stimulation, Vagus Nerve Stimulation).

”Novel Drug Developmental Strategies for Treatment-Resistant Depression” is a narrative literature review with a descriptive and synthetic approach. Due to the lack of a detailed methodological framework, it does not qualify as a systematic review. The authors primarily focus on novel drugs, including ketamine, dextromethorphan, NMDA receptor agonists and antagonists, agents targeting AMPA and GABA-A receptors, as well as compounds affecting the monoaminergic and cholinergic systems. The review highlights emerging strategies and concepts in the development of antidepressant therapies.

”Pharmacological Treatments for Patients with Treatment-Resistant Depression” is a systematic literature review that focuses on comparing the efficacy, tolerability, and onset of action of various antidepressants and augmentation strategies. The authors conducted a search in two

databases, PubMed and PsycINFO, and selected 71 randomized cotrolled trials, that met the specified inclusion criteria. The criteria for inclusion in this review specified that studies must be randomized controlled trials involving adult patients (over 18 years old) diagnosed with major depressive disorder (MDD) who had not responded to at least one antidepressant. To focus the review, only the most extensively researched medications were included, specifically antidepressants, SGAs, lithium, thyroid hormone, lamotrigine, ketamine, and esketamine.

Electroconvulsive Therapy:

Electroconvulsive therapy (ECT) is considered the most effective therapeutic intervention for treatment-resistant depression (TRD), despite the incomplete understanding of its neurophysiological mechanisms. The procedure involves delivering high-frequency electrical impulses to the cerebral cortex, typically unilaterally (targeting the nondominant hemisphere and the vertex) or bilaterally (in the region of both temporal lobes). Repeated electrical stimulation leads to the synchronization of neuronal activity and induces a generalized tonic-clonic seizure, which spontaneously resolves within 30–60 seconds. In the standard therapeutic protocol, ECT sessions are conducted 2–3 times per week, and a full treatment course typically includes 6 to 18 sessions. Data from the CORE study indicate that more than half of the patients experience significant symptom improvement as early as the first week of therapy. Other studies suggest that ECT can be effective in more than 50% of individuals who previously did not respond to at least one adequate trial of pharmacological treatment. Meta-analyses have demonstrated the superiority of ECT over placebo, sham therapy, and standard antidepressant treatment. Despite its high therapeutic efficacy, the use of ECT remains limited due to stigma, largely stemming from negative portrayals in the media, and concerns about potential side effects, particularly those affecting cognitive function. Additionally, limited access to the procedure further contributes to its infrequent use—according to one study, only 0.25% of patients with mood disorders in the United States received electroconvulsive therapy. It is important to emphasize that advancements in procedural techniques, such as individual adjustment of seizure thresholds, the use of more tolerable anesthetic agents, and improved perioperative care, have significantly reduced the risk of adverse effects. In 2001, the American Psychiatric Association issued recommendations to broaden the use of ECT beyond situations deemed "last resort" and to include cases of severe depressive episodes resistant to pharmacological treatment or those posing a threat to life. (Voineskos et al., 2020).

The placement of electrodes plays a crucial role in the application of electroconvulsive therapy (ECT), influencing the path of current propagation through brain tissues. Three main electrode locations are distinguished: the right upper frontal lobe (RUL), bitemporal placement, and

bifrontal placement, with the latter being variants of bilateral localization. Historically, ECT was applied in a bilateral configuration, with electrodes positioned on the sides of the head, which involved the flow of current through the left temporal lobe. Due to potential adverse effects associated with this location, particularly concerning language function, practitioners often prefer to start treatment with the RUL placement, positioning the electrodes on the right temporal lobe and along the midline above the head. In left-handed patients, who may have a dominant right hemisphere, there is the option of unilateral electrode placement on the left side to minimize the risk of negative cognitive effects. Bifrontal electrode placement on the forehead is also an option.

The parameters of the electric current, such as amplitude and pulse shape, significantly influence the speed of symptom alleviation and the risk of adverse effects. In modern clinical practice, the standard current amplitude ranges from 800 to 900 mA, depending on the device and protocols used. The pulse shape can be rectangular, with pulse widths ranging from 0.25 to 1 ms, and pulse series are typically monophasic, with the possibility of changing polarity. In practice, titration is also used to individualize electric dosing by increasing the number of pulses in a series.

In the clinical context, treatment often begins with RUL placement or, in urgent cases, with bitemporal or bifrontal configurations, as bilateral stimulation tends to yield quicker therapeutic effects, although it is associated with a higher risk of adverse effects. A systematic review of ECT in the UK found that bilateral ECT is generally more effective in alleviating depressive symptoms compared to unilateral ECT. However, study results, including randomized controlled trials, suggest that short pulse RUL ECT may be comparable in efficacy to short pulses of bifrontal and bitemporal ECT.

Despite concerns regarding acute negative effects on cognitive functions following ECT, it is generally accepted that cognitive-related adverse effects, particularly concerning memory, return to baseline within six months post-treatment. The treatment protocol may start with bilateral ECT and then transition to RUL if adverse effects occur, or vice versa—beginning with high-dose RUL ECT in initial therapy and subsequently using bilateral ECT for maintenance purposes.

In recent years, a novel approach to electrode placement known as focal electrically administered seizure therapy (FEAST) has been investigated to reduce cognitive side effects. FEAST employs unilateral stimulation and asymmetrical frontal electrode placement, where a large posterior electrode (cathode) is positioned in front of the right motor cortex, and a small anterior electrode (anode) is placed above the right orbitofrontal cortex. This configuration aims

to concentrate seizure induction in the right prefrontal cortex, potentially leading to reduced cognitive-related adverse effects. (Kritzer et al., 2023)

Results

In study, performed by (Nuñez et al., 2022) a total of 6,322 records were retrieved, with 69 studies included in the final analysis. To visualize the network geometry, a network plot was generated. Nine studies (N = 1,450) compared head-to-head drug treatments (Bauer et al., 2013; Cheon et al., 2017; Dorée et al., 2007; Dunner et al., 2007; Nierenberg et al., 2006; Raeisi et al., 2006; Schindler and Anghelescu, 2007; Shahal et al., 1996; Trivedi et al., 2006), with treatment durations of up to 12 weeks. Fifty-one studies (52 cohorts) compared medications to placebo (Abolfazli et al., 2011; Appelberg et al., 2001; Barbee et al., 2011; Barbosa et al., 2003; Bauer et al., 2009; Baumann et al., 1996; Berman et al., 2007; Browne et al., 1990; Carpenter et al., 2002; Chaput et al., 2008; Corrigan et al., 2000; Corya et al., 2006; Cusin et al., 2013; DeBattista et al., 2003; Dunlop et al., 2007; Durgam et al., 2016; Earley et al., 2018; El-Khalili et al., 2010; Fava et al., 2018, 2012, 2005; Gitlin et al., 1987; GlaxoSmithKline, 2009; Gulrez et al., 2012; Han et al., 2015; Heninger et al., 1983; Kamijima et al., 2013; Katona et al., 1995; Keitner et al., 2009; Kessler et al., 2018; Landén et al., 1998; Madhoo et al., 2014; Mahmoud et al., 2007; Marcus et al., 2008; McIntyre et al., 2007; Nierenberg et al., 2003; Normann et al., 2002; Papakostas et al., 2015; Patkar et al., 2006; Berman et al., 2009; Ravindran et al., 2008; Reeves et al., 2008; Richards et al., 2016; Santos et al., 2008; Schöpf et al., 1989; Stein and Bernadt, 1993; Thase et al., 2007, 2015b, 2015a; Trivedi et al., 2013; Zusky et al., 1988), with a total sample size of N = 10,701, and treatment durations ranging from 48 hours to 16 weeks. Additionally, nine multi-arm studies were included (Fang et al., 2011; Franco-Chaves et al., 2013; Joffe et al., 1993; Joffe and Singer, 1990, 2006; Shelton et al., 2001; Shelton et al., 2005; Yoshimura et al., 2014, 2012), with a total sample size of N = 972 and treatment durations of 2 to 8 weeks. The primary analyses focused on direct effect comparisons (response, remission, and discontinuation rates) for each pharmacological class versus placebo. Regarding response rates, 65 studies included data from 19 treatments (medications N = 7,669 and placebo N = 4,746), which consisted of 7 atypical antipsychotics (AAs): aripiprazole (n = 1,147), brexpiprazole (n = 599), cariprazine (n = 963), olanzapine with fluoxetine (n = 668), quetiapine (n = 909), risperidone (n = 262), and ziprasidone (n = 71); 2 mood stabilizers: lithium (n = 469) and lamotrigine (n = 115); buspirone (n = 441); 3 antidepressants: bupropion (n = 492), mirtazapine (n = 225), nortriptyline (n = 23); 4 dopaminergic compounds: pramipexole (n = 147), lisdexamfetamine (n = 568), modafinil (n = 284), and methylphenidate (n = 103); and

thyroid hormones (T3, n = 114; T4, n = 69). In terms of efficacy, T3, T4 nortriptyline, aripiprazole, risperidone, brexpiprazole, quetiapine, lithium, modafinil, olanzapine (fluoxetine), cariprazine, and lisdexamfetamine demonstrated statistically significant efficacy compared to placebo, with relative risks (RRs) ranging from 1.18 (1.03–1.37) for lisdexamfetamine to 1.90 (1.16–3.11) for T3. Heterogeneity (I2 = 9.8%, p = 0.541) and inconsistency (p = 0.085) were not statistically significant. A sensitivity analysis excluding specific studies did not alter the main results. A sub-analysis of lithium augmentation in studies with treatment durations of ≤ 3 weeks revealed significantly higher response rates compared to placebo (RR = 2.43, 95% CI: 1.45–4.07, p < 0.0007). A post-hoc sub-analysis of thyroid augmentation in studies with durations of ≤ 3 weeks showed no statistically significant difference compared to placebo (RR = 1.79, 95% CI: 0.48–6.67). Regarding remission rates, 39 studies (40 cohorts) included 19 treatments (medications N = 6,279 and placebo N = 3,965), consisting of 7 AAs (aripiprazole, n = 1,123; brexpiprazole, n = 599; cariprazine, n = 963; olanzapine with fluoxetine, n = 658; quetiapine, n = 667; risperidone, n = 250; ziprasidone, n = 71), 2 mood stabilizers (lithium, n = 106; lamotrigine, n = 30), 3 antidepressants (bupropion, n = 326; mirtazapine, n = 225; nortriptyline, n = 23), buspirone (n = 332), 4 dopaminergic compounds (pramipexole, n = 43; lisdexamfetamine, n = 497; modafinil, n = 215; methylphenidate, n = 30), and thyroid hormones (T3, n = 73; T4, n = 48).No statistically significant heterogeneity (I2 = 2.4%, p = 0.473) or inconsistency (p = 0.306) was observed. For all-cause discontinuation, 53 studies (54 cohorts) assessed 17 treatments (medications N = 7,223 and placebo N = 4,617), with a total of 1,642 discontinuation events. Discontinuation rates were significantly higher for ziprasidone (RR = 20.12, 95% CI: 1.17–344.58), mirtazapine (RR = 4.12, 95% CI: 1.97–8.63), and cariprazine (RR = 1.72, 95% CI: 1.09–2.73) compared to placebo. No significant heterogeneity (I2 = 17.3%, p = 0.251) or inconsistency (p = 0.167) was found. (Nuñez et al., 2022)

Antidepressants and Buspirone: Pharmacological augmentation with other antidepressants (ADs), such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), or tricyclic antidepressants (TCAs), in treatment-resistant depression (TRD) has been insufficiently studied, particularly regarding potential synergistic effects and the risk of adverse events. Altamura and colleagues conducted a randomized placebo-controlled trial (RCT) that demonstrated the efficacy of low-dose intravenous (IV) citalopram augmentation to oral SSRIs in 36 non-responders with major depressive disorder (MDD). Similarly, an open-label study reported that buspirone augmentation was effective in patients with poor response to SSRIs. Additionally, Taylor and Prather demonstrated the effectiveness of nefazodone augmentation in a small cohort of 11 patients with TRD and high

anxiety levels. In contrast, a large double-blind RCT by Licht and Qvitzau found that sertraline monotherapy at 100 mg/day had comparable effects to mianserin as an add-on therapy. A more recent RCT also found that mirtazapine did not show superiority over placebo in improving depressive symptoms in a large sample of TRD patients (n = 431). Short-term augmentation with low-dose IV citalopram or clomipramine has been shown to be more effective than placebo augmentation in 54 patients who did not respond to SSRIs. Three studies compared the efficacy of continuing AD monotherapy versus augmentation with TCAs, SSRIs, or lithium. Fava and colleagues published two double-blind studies involving fluoxetine-resistant MDD patients who were randomly assigned to high-dose fluoxetine, fluoxetine plus desipramine, or fluoxetine plus lithium. In the first study (n = 41), high-dose fluoxetine was more effective than the augmentative treatments. However, the second study (n = 101) showed no significant differences in response rates between the three treatment groups. Finally, a recent randomized open-label study (n = 104) found a higher response rate with add-on citalopram compared to add-on lithium in MDD patients who had not responded to 10 weeks of imipramine treatment. (Caldiroli et al., 2021)

Switching to a different antidepressant is a viable strategy for patients who fail to respond to initial treatment. This approach was investigated in Level 2 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study, which compared switching to bupropion (n = 239), sertraline (n = 238), or venlafaxine (n = 250) among patients with major depressive disorder (MDD) who had an inadequate response to citalopram and opted to switch therapies. Response rates for bupropion, sertraline, and venlafaxine were 26.1%, 26.7%, and 28.2%, respectively, while remission rates were 21.3%, 17.6%, and 24.8%, respectively, with no statistically significant differences between groups ($\chi^2 = 3.649$, df = 2, $p = 0.16$). Additionally, the three treatments showed no significant differences in time to remission ($\chi^2 = 0.38$, $p = 0.93$), time to response ($\chi^2 = 0.65$, $p = 0.72$), or tolerability profiles. In another study, Thase et al. evaluated the outcomes of switching between imipramine and sertraline after nonresponse. Among participants, 55% of 117 patients who failed to respond to sertraline achieved a response after switching to imipramine, while 63% of 51 patients who failed to respond to imipramine responded to sertraline ($\chi^2 = 1.96$, $p = 0.16$). Remission rates were also similar, with 35% achieving remission in the sertraline group versus 30% in the imipramine group ($\chi^2 = 0.94$, $p = 0.33$). In Level 3 of STAR*D, Fava et al. examined a sample of 235 participants who did not respond to citalopram, followed by either augmentation or switching strategies. Patients were randomized to monotherapy with either mirtazapine (n = 114) or nortriptyline (n = 121). Response rates were 13.4% for mirtazapine and 16.5% for nortriptyline ($p = 0.57$), while

remission rates were 8% and 12.4%, respectively (p = 0.45). No significant differences in tolerability were observed between the two treatments. In a separate study, Fang et al. assessed remission rates among patients who switched to mirtazapine (36.4% of 55 patients), venlafaxine (42% of 50 patients), or paroxetine (46.7% of 45 patients) in a cohort of 150 participants with prior nonresponse to two antidepressants. The differences in remission rates were not statistically significant ($\chi^2 = 1.097$, df = 2, p = 0.578). (Ruberto et al., 2020)

Combining Antidepressants Versus Antidepressant Monotherapy: The VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) study evaluated three treatment strategies in a randomized, open-label design involving 1,522 adult Veterans with inadequate responses to at least one antidepressant. The strategies included switching to bupropion, augmenting with bupropion, or augmenting with aripiprazole. Results showed that response rates for bupropion augmentation (65.6% of 506 participants) were not significantly higher than switching to bupropion monotherapy (62.4% of 511 participants; RR, 1.05 [95% CI, 0.96–1.15]; p = 0.29). Remission rates were also comparable at 26.9% and 22.3%, respectively (RR, 1.20 [95% CI, 0.97–1.50]; p = 0.09). Results regarding aripiprazole augmentation are discussed in subsequent sections. Lam et al. compared the efficacy of bupropion monotherapy (n = 17), citalopram monotherapy (n = 12), and a combination of bupropion with citalopram (n = 32) in 61 patients who previously failed either antidepressant. The combination group achieved significantly higher remission rates (28%) compared to the monotherapy groups (7%, p < 0.05). In Level 2 of the STAR*D study, Trivedi et al. examined combining bupropion with citalopram (n = 279) versus augmenting citalopram with buspirone (n = 286) among 565 participants with inadequate responses to citalopram. Response rates were 31.8% for the bupropion-citalopram combination and 26.9% for buspirone augmentation (p = 0.21), while remission rates were similar at 29.7% and 30.1%, respectively ($\chi^2 = 0.01$, p = 0.93). Adverse effects such as headache and insomnia were generally mild to moderate in severity, and combining bupropion with other antidepressants did not significantly increase adverse event frequency or severity. A double-blind study by Nelson et al. compared a combination of fluoxetine and desipramine (n = 13) to fluoxetine monotherapy (n = 14) or desipramine monotherapy (n = 12) in 39 patients who failed to respond to at least one antidepressant. The combination therapy demonstrated superior efficacy, with response rates of 35.7% compared to 7.7% and 16.7% for fluoxetine and desipramine monotherapy, respectively. Remission rates were also significantly higher with the combination (53.8% vs. 7.1% and 0%, $\chi^2(6) = 24.01$, p = 0.0005). Symptom improvement was observed as early as two weeks into treatment. In Level 4 of the STAR*D study, the combination of mirtazapine and venlafaxine (n = 51) was

compared to tranylcypromine monotherapy (n = 58) in 109 patients who failed three previous antidepressant trials. No significant differences were observed in remission rates (13.7% vs. 6.9%), response rates (23.5% vs. 12.1%), time to remission, or tolerability between the two groups. In contrast, an open-label study by Navarro et al. compared mirtazapine and venlafaxine combination therapy (n = 56) to imipramine monotherapy (n = 56) in patients unresponsive to venlafaxine. Imipramine monotherapy was significantly more effective, with remission rates of 71.43% versus 39.28% for the combination therapy ($\chi^2 = 11.71$, $p = 0.001$). A double-blind study by Carpenter et al. evaluated the addition of mirtazapine versus placebo to ongoing antidepressant therapy in 26 patients with previous nonresponse. The mirtazapine group achieved significantly lower HAM-D scores at the endpoint (10.7 ± 7.0 vs. 17.3 ± 8.2; $p = 0.017$), with response rates of 63.6% compared to 20% ($p = 0.043$) and remission rates of 45.5% versus 13.3% ($p = 0.068$). However, a phase III study by Kessler et al. found no significant differences between adding mirtazapine (n = 241) versus placebo (n = 239) to ongoing treatment with an SSRI or SNRI in 480 patients. Response rates were 44% for mirtazapine and 36% for placebo ($p = 0.10$), while remission rates were 29% and 24%, respectively ($p = 0.27$). Tolerability was similar between the two groups. (Ruberto et al., 2020)

Aripiprazol: Aripiprazole has been the most extensively studied second-generation antipsychotic (SGA) for augmentation in treatment-resistant depression (TRD). An initial retrospective chart review highlighted the effectiveness of aripiprazole augmentation in 30 TRD patients. A subsequent retrospective study involving 38 TRD patients with a mixed specifier diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), demonstrated significant improvements in both the Montgomery-Åsberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) scores. Eight open-label studies have reported positive outcomes with aripiprazole augmentation. Two studies, each involving up to 15 TRD patients, confirmed the efficacy of aripiprazole as an adjunct to antidepressant (AD) treatment. Fabrazzo and colleagues showed that a fixed dose of aripiprazole (5 mg/day) effectively augmented tricyclic antidepressants (TCAs) in 35 TRD patients. Furthermore, adjunctive aripiprazole was found to be equally effective when added to paroxetine or sertraline in 24 major depressive disorder (MDD) patients, and low-dose aripiprazole also demonstrated effectiveness in a cohort of 9 TRD patients from Taiwan. A 12-week prospective open-label multicenter study reported a significant improvement in depressive symptoms, with a response rate greater than 50% and a remission rate of approximately 40% for those receiving aripiprazole augmentation. A recent randomized open-label study by Horikoshi and colleagues compared low-dose (3 mg/day) and high-dose (12

mg/day) aripiprazole augmentation in TRD patients, demonstrating significant differences in the speed of response, with the high-dose group responding earlier. Three large multicenter randomized controlled trials (RCTs), conducted by the same research group, further confirmed the efficacy of aripiprazole augmentation in TRD patients, with sample sizes of 362, 324, and 349, respectively. In contrast, another RCT failed to show superiority for low-dose aripiprazole (2–5 mg/day) compared to placebo. This study (n = 221) was re-analyzed, and the findings were reported in two additional papers. The first demonstrated that some non-responders to 2 mg/day showed improvement with a dose of 5 mg/day, while the second found a statistically significant improvement in the depression subscale of the Kellner Symptom Questionnaire, though no significant effects were observed in the anxiety and hostility subscales. Another RCT involving 181 patients with late-life depression found that a maximum dose of 15 mg/day of aripiprazole was effective as an augmentation strategy. Finally, the ADMIRE study, conducted by a Japanese research group, randomized 540 patients to receive either a placebo, a fixed dose of 3 mg/day, or a flexible dose of 3–15 mg/day of aripiprazole. Both active treatment groups showed greater improvements in depressive symptoms compared to placebo, which was also confirmed by a sub-analysis focused on core depressive symptoms. (Caldiroli et al., 2021) Aripiprazole is FDA-approved as an augmentation therapy for MDD at doses ranging from 2 mg/day to 15 mg/day, with evidence suggesting efficacy as early as two weeks into treatment. In a rater-blind study, Han et al. compared aripiprazole augmentation (n = 52) with switching to another antidepressant (n = 49) in 101 patients unresponsive to a single antidepressant during the current depressive episode. Aripiprazole was initiated at 2–5 mg/day, titrated by increments of 2–5 mg/day, up to a maximum of 15 mg/day. Augmentation with aripiprazole demonstrated superior outcomes, with response rates of 60% versus 32.6% ($p = 0.0086$) and remission rates of 54% versus 19.6% ($p = 0.0005$). In a double-blind trial, Marcus et al. evaluated aripiprazole augmentation (n = 191) against placebo augmentation (n = 190) in 381 participants who failed to respond to antidepressant therapy. Aripiprazole augmentation yielded significantly higher remission rates (25.4% vs. 15.2%; $p = 0.016$) and response rates (32.4% vs. 17.4%; $p < 0.001$). The mean endpoint dose was 11.0 mg/day, with dosing ranging from 2 to 20 mg/day. Similarly, Berman et al. reported that aripiprazole augmentation (n = 177) led to significantly greater response rates (46.6% vs. 26.6%; $p < 0.001$) and remission rates (36.8% vs. 18.9%; $p < 0.001$) compared to placebo (n = 172) in 349 patients unresponsive to antidepressants. The mean endpoint dose in this trial was 13.9 mg/day, with a dose range of 2 to 20 mg/day. The VAST-D study, as discussed earlier, compared switching to bupropion (n = 511), augmenting with bupropion (n = 506), and augmenting with aripiprazole (n = 505). Aripiprazole augmentation

demonstrated significantly higher response rates compared to both bupropion augmentation (74.3% vs. 65.6%; RR, 1.13 [95% CI, 1.04–1.23]; p = 0.003) and switching to bupropion (74.3% vs. 62.4%; RR, 1.19 [95% CI, 1.09–1.29]; p < 0.001). Remission rates with aripiprazole were significantly higher than switching to bupropion (28.9% vs. 22.3%; RR, 1.03 [95% CI, 1.05–1.60]; p = 0.02), but not significantly different from bupropion augmentation (28.9% vs. 26.9%; RR, 1.08 [95% CI, 0.88–1.31]; p = 0.47). In another study, Yoshimura et al. compared aripiprazole augmentation of paroxetine with aripiprazole augmentation of sertraline in 26 patients unresponsive to two antidepressants from different classes. There was no significant difference in response rates (27.7% vs. 15.4%; p = 0.475) between the groups. These findings collectively suggest that aripiprazole's efficacy as an augmentation agent is independent of the specific background antidepressant. Contrastingly, a double-blind study by Fava et al. reported no significant difference between aripiprazole augmentation at 2 mg/day (n = 56) and placebo (n = 169) in a sample of 225 participants. Response rates were 18.5% for aripiprazole and 17.4% for placebo, with a weighted difference of 5.62% ([95% CI, −2.69–13.94]; p = 0.18). Remission rates were 7.41% for aripiprazole and 9.58% for placebo, with a weighted difference of 2.30% ([95% CI, −4.35–8.94]; p = 0.49). This discrepancy may suggest reduced efficacy at low doses of aripiprazole. The most common side effect of aripiprazole is akathisia (25% vs. 4% with placebo), which can occur even at doses as low as 2 mg/day. Other adverse events include restlessness (12% vs. 2% with placebo), insomnia (8% vs. 2%), fatigue (8% vs. 4%), and blurred vision (5% vs. 1%). Higher doses are associated with increased frequency and severity of adverse effects. Overall, aripiprazole in doses ranging from 2 mg/day to 20 mg/day is generally well-tolerated as an augmentation strategy for MDD. (Ruberto et al., 2020) In a randomized trial conducted by Mohamed and collaborators, aripiprazole augmentation was significantly more effective than switching to bupropion monotherapy in achieving remission. However, the comparative efficacy of augmentation strategies involving these two compounds did not reach statistical significance. (Caldiroli et al., 2021)

Other SGAs:

Brexpiprazole, a molecule with pharmacological similarities to aripiprazole, has shown promising results in treatment-resistant depression (TRD). Two large randomized controlled trials (RCTs) by Thase and colleagues demonstrated that brexpiprazole was superior to placebo at higher doses of 2 or 3 mg/day, but not at 1 mg/day. More recently, an open-label study involving 51 TRD patients who had not responded to prior augmentation strategies found that brexpiprazole significantly reduced Montgomery-Åsberg Depression Rating Scale (MADRS) scores, regardless of the previous augmentation approach. Another double-blind RCT

confirmed that brexpiprazole outperformed placebo in reducing MADRS scores in 393 TRD patients. In a three-phase study of 489 patients, augmentative risperidone showed short-term improvements in depressive symptoms but did not demonstrate superior long-term efficacy compared to placebo. A sub-analysis of elderly patients (n = 89) who had not responded to citalopram revealed significant improvement with risperidone augmentation. Another RCT by Mahmoud and colleagues reported significant improvements in depressive symptoms in patients treated with risperidone compared to placebo. In an open-label study of 20 TRD patients, Papakostas and colleagues demonstrated the efficacy of ziprasidone as an adjunct to selective serotonin reuptake inhibitors (SSRIs). Additionally, two small open-label studies suggested that quetiapine may be beneficial as an augmentation treatment in TRD. The combination of fluoxetine and olanzapine was shown to be more effective than either olanzapine or fluoxetine monotherapy in a double-blind, small sample RCT. These findings were supported by an open-label study assessing the effects of olanzapine augmentation in 11 TRD patients treated with milnacipran. Finally, a recent RCT involving 530 patients failed to demonstrate the efficacy of cariprazine augmentation in individuals with major depressive disorder (MDD) who had inadequate responses to previous antidepressant treatments. (Caldiroli et al., 2021) No significant differences in efficacy were identified between quetiapine extended-release (XR) at a dosage of 300 mg/day and lithium as adjunctive treatments in a cohort of 557 patients with treatment-resistant depression (TRD). Additionally, in a separate double-blind randomized controlled trial (RCT), brexpiprazole demonstrated superiority over placebo, whereas quetiapine did not. Gobbi and colleagues reported that both antidepressant (AD) augmentation and the addition of a second-generation antipsychotic (SGA) such as olanzapine, risperidone, quetiapine, or aripiprazole resulted in improved depressive symptoms over time, with SGAs showing greater efficacy compared to ADs. (Caldiroli et al., 2021)

The combination of olanzapine and fluoxetine (OFC) was the first medication approved by the U.S. FDA for the treatment of treatment-resistant depression (TRD). In this context, “combination” refers to the concurrent administration of two medications, whereas “augmentation” typically describes the use of a second non-antidepressant medication (e.g., an atypical antipsychotic) alongside an antidepressant. Shelton et al. conducted a study comparing the OFC combination (n = 9) to olanzapine monotherapy(n = 6) and fluoxetine monotherapy (n = 9) in 24 patients who had not responded to at least one prior antidepressant. The response rate in the combination group (60%) was significantly higher than that in the olanzapine monotherapy group (0%; p = 0.03), though not significantly higher than the fluoxetine monotherapy group (10%; p = 0.11). However, the OFC group demonstrated significantly

greater improvement from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) compared to both monotherapy groups: −13.6 vs. −2.8 (olanzapine monotherapy; p = 0.03) and −13.6 vs. −1.2 (fluoxetine monotherapy; p = 0.006). In a larger double-blind study, Thase et al. compared OFC (n = 200) with olanzapine monotherapy (n = 199) and fluoxetine monotherapy (n = 206) in patients who had failed fluoxetine and one additional antidepressant in their current depressive episode. The OFC group showed a significantly greater reduction in MADRS total scores (−14.5) compared to olanzapine monotherapy (−7.0; p < 0.001) and fluoxetine monotherapy (−8.6; p < 0.001). Additionally, remission rates were higher for the OFC group (27%) compared to fluoxetine monotherapy (17%) and olanzapine monotherapy (15%). However, Shelton et al. conducted another study with contradictory findings. This study compared OFC (n = 146) to olanzapine (n = 144), fluoxetine (n = 142), and nortriptyline (n = 68) monotherapies in a sample of 500 patients who had failed at least one SSRI. In this trial, the OFC group demonstrated a significantly greater reduction in MADRS scores than the olanzapine group at study endpoint (p = 0.005), but no other significant differences were observed across the other treatment groups. A further study by Corya et al. questioned the comparative efficacy of OFC in a sample of patients who had failed to respond to both an SSRI and venlafaxine. Treatment arms included OFC (n = 243), olanzapine monotherapy (n = 62), fluoxetine monotherapy (n = 60), venlafaxine monotherapy (n = 59), and a lower dose OFC group (n = 59) containing 1 mg/day olanzapine and 5 mg/day fluoxetine(instead of the typical 6 mg/day olanzapine and 25 mg/day fluoxetine). The OFC group (43.3%) demonstrated a significantly higher response rate than olanzapine monotherapy (25.4%; p = 0.017), but no significant difference was observed compared to the fluoxetine monotherapy (33.9%), venlafaxine (50.0%), or low-dose OFC (36.4%) groups. Similarly, the OFC group showed a significantly higher remission rate (29.9%) compared to olanzapine monotherapy (13.6%; p = 0.013), but no significant difference was found between OFCand fluoxetine monotherapy (17.9%), venlafaxine (22.4%), or low-dose OFC (20.0%) groups. These findings suggest mixed results regarding the efficacy of the OFC combination, with some studies showing significant benefits over monotherapy, while others report more modest or inconclusive results. The combination of olanzapine and fluoxetine (OFC) has been associated with metabolic changes, including hyperglycemia, dyslipidemia, and weight gain. After 12 weeks of treatment, 34.1% of patients taking OFC had a random glucose level of 140 mg/dl or higher, compared to 3.6% of those on placebo. Additionally, 36.2% of patients on OFC had a non-fasting total cholesterol level of 200 mg/dl or higher, compared to 9.9% of patients on placebo. These metabolic changes may increase the risk of cardiovascular and cerebrovascular adverse events in affected patients.

Quetiapine, another second-generation antipsychotic (SGA), has demonstrated efficacy in treating depressive symptoms in patients who have not responded to prior antidepressant treatments. It is FDA-approved as an augmentation agent for depression. In some cases, quetiapine shows efficacy within one week of treatment. It is administered in doses of 150 mg/day or 300 mg/day. In a placebo-controlled study by Cutler et al., both the 150 mg/day (n = 152) and 300 mg/day (n = 152) quetiapine augmentation groups showed significantly higher response rates (54.4% and 55.1%, respectively; $p < 0.01$) compared to placebo (36.2%) in patients who had failed fewer than two antidepressants in the current depressive episode. However, only the 300 mg/day group (32.0%; $p < 0.05$) demonstrated a significantly higher remission rate than placebo (20.4%), while the 150 mg/day group (26.5%) did not show a significant difference ($p = 0.267$). In a similar double-blind study by El-Khalili et al., 300 mg/day quetiapine (n = 150) was significantly more effective than placebo (n = 148), with a response rate of 58.9% compared to 46.2% for placebo ($p < 0.05$) and a remission rate of 42.5% compared to 24.5% for placebo ($p < 0.01$). The 150 mg/day quetiapine group (n = 148) did not show a significant difference in response rates (51.7% vs. 46.2%; $p = 0.329$) but trended towards a higher remission rate (35.0% vs. 24.5%; $p = 0.059$). Another study by Bauer et al. found that the 300 mg/day dose (57.8%; $p < 0.05$ vs. placebo) was significantly more effective than placebo (46.3%) in terms of response, while the 150 mg/day dose (55.4%) did not differ significantly from placebo. The 300 mg/day group had a remission rate of 31.1% ($p = 0.126$ vs. placebo), while the 150 mg/day group showed a 36.1% remission rate ($p < 0.05$ vs. placebo), compared to 23.8% for placebo. However, a study by Hobart et al. did not show a significant difference between quetiapine augmentation (n = 100) and placebo augmentation (n = 206) in a sample of patients who had failed to respond to one to three antidepressants. Response rates were 8.1% for the quetiapine group and 6.8% for placebo ($p = 0.60$), with remission rates of 2.0% and 4.4%, respectively ($p = 0.39$). As with OFC, quetiapine can also cause metabolic disturbances, including hyperglycemia, dyslipidemia, and weight gain. In patients taking 300 mg/day quetiapine, 12% shifted from normal blood glucose levels to 126 mg/dl or higher, compared to 7% for those taking 150 mg/dayquetiapine and 6% for those on placebo. Furthermore, 16% of patients on quetiapine experienced a rise in total cholesterol to 240 mg/dl or higher, compared to 7% of those on placebo. Additionally, 5% of patients on quetiapine gained at least 7% of their body weight, compared to 2% of those on placebo. Brexpiprazole is FDA-approved as an augmentation agent for the treatment of depression. A phase III study by Thase et al. evaluated the efficacy of a 2 mg/day dose of brexpiprazole (n = 175) in patients with inadequate response to at least one antidepressant. The brexpiprazole group showed a

significantly higher response rate (23.4%) compared to placebo (15.7%; LS mean = 1.54 [95% CI, 1.01–2.35]; p = 0.0429). While the remission rate (14.9%) for the brexpiprazole group was numerically higher than placebo (9.0%), the difference was not statistically significant (LS mean = 1.67 [95% CI, 0.97–2.90]; p = 0.0671). Additionally, brexpiprazole resulted in a significantly greater reduction in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score (−8.36) compared to placebo (−5.15; LS mean = −3.21 [95% CI, −4.87 to −1.54]; p = 0.0002). In another phase III study by Thase et al., the efficacy of 1 mg/day (n = 211) and 3 mg/day (n = 213) doses of brexpiprazole was assessed in patients who had failed 1 to 3 antidepressants. Both doses showed significantly higher response rates than placebo (n = 203), but the remission rates were not significantly different. The response rates were 23.2% for the 1 mg/day group (LS mean = 1.69 [95% CI, 1.14–2.50]; p = 0.0094) and 23.0% for the 3 mg/day group (LS mean = 1.65 [95% CI, 1.09–2.50]; p = 0.0162), compared to 14.3% for placebo. The 3 mg/day dose showed a significantly greater decrease in MADRS score (−8.29) compared to placebo (−6.33; LS mean = −1.95 [95% CI, −3.39 to −0.51]; p = 0.0079), whereas the 1 mg/day group showed no significant difference from placebo (−7.64 vs. −6.33; LS mean = −1.30 [95% CI, −2.73 to 0.13]; p = 0.0737). Brexpiprazole may show efficacy in as little as one week. In contrast, Hobart et al. found that brexpiprazole augmentation (2–3 mg/day, n = 197) did not result in significantly higher response (10.5% vs. 6.8%; p = 0.22) or remission rates (6.8% vs. 4.4%; p = 0.33) compared to placebo (n = 206) in patients who had failed 1 to 3 antidepressants. However, brexpiprazole was associated with a significantly greater change in MADRS score from baseline to endpoint (mean change of −6 vs. −4.6 in the placebo group; LS mean = −1.48 [95% CI, −2.56 to −0.39]; p = 0.0078). The most common adverse events were weight gain (7% vs. 2% with placebo) and akathisia (9% vs. 2% with placebo), with akathisia appearing to be dose-dependent. Risperidone, although showing positive results as an augmentation agent for unipolar depression in several studies, is not FDA-approved for this indication. In a study by Mahmoud et al., patients receiving risperidone (n = 137) showed higher response rates (46.2%) compared to placebo (n = 131) (29.5%; p = 0.004). The same pattern was seen for remission rates (24.5% vs. 10.7%; p = 0.004). Similarly, Keitner et al. found that risperidone (n = 64) led to higher response (54.8%) and remission (51.6%) rates compared to placebo (33.3% response, 24.2% remission) in a sample of 94 patients. In a double-blind study by Reeves et al., risperidone (n = 12) was significantly more effective than placebo (n = 11) in patients who failed to respond to two antidepressants. The mean change in MADRS score at week 6 was −21.68 (SE = 2.28) for the risperidone group, compared to −11.39 (SE = 2.53) for the placebo group (p = 0.0087). A pilot study by Fang et al. compared the efficacy of risperidone (n = 45)

and several other augmentation agents (thyroid hormone, buspirone, valproate, trazodone) in patients who failed at least one antidepressant. There were no significant differences in response (46.7% for risperidone, 61.5% for valproate, 56.5% for buspirone, 61.7% for trazodone, 58.3% for thyroid hormone; p = 0.601) or remission rates (26.7% for risperidone, 48.7% for valproate, 32.6% for buspirone, 42.6% for trazodone, 37.5% for thyroid hormone; p = 0.255). Risperidone is generally well-tolerated, with Keitner et al. reporting no difference in the number of adverse events between risperidone and placebo. Common side effects include dry mouth, headache, and somnolence. Ziprasidone, another SGA, has shown some efficacy as an augmentation agent for treatment-resistant depression (TRD) but is not FDA-approved for this use. In a study by Papakostas et al., augmentation of escitalopram with ziprasidone (n = 71) resulted in a response rate of 35.2%, significantly higher than the placebo group (20.5%; p = 0.04). However, the remission rate for the ziprasidone group (38.0%) was not significantly different from the placebo group (30.8%; p = 0.32). Another study by Papakostas et al. compared ziprasidone monotherapy (n = 21) to placebo (n = 25) and found no significant differences in response rates (5% vs. 7%; p = 0.59) or remission rates (7% vs. 10%; p = 0.73). (Ruberto et al., 2020)

Mood Stabilizers:

Lithium: Lithium augmentation remains one of the most extensively studied strategies for managing treatment-resistant depression (TRD) in patients undergoing ongoing antidepressant (AD) therapy. An early double-blind randomized controlled trial (RCT) involving 34 patients resistant to tricyclic antidepressants (TCAs) reported significant antidepressant effects with high-dose lithium (750 mg/day) but not with lower doses (250 mg/day). In contrast, a later study of 92 TRD patients found no significant differences in outcomes between lithium and placebo in 35 individuals resistant to nortriptyline treatment. Another RCT evaluated the efficacy of lithium augmentation during a 4-month continuation phase in 27 TRD patients and observed relapses only in the placebo group, suggesting that lithium responders should continue treatment for at least 6 months or longer. Subsequently, Bschor and collaborators followed 22 participants from this sample, finding no significant differences in 1-year recurrence rates between lithium and placebo groups, concluding that lithium should be maintained for a minimum of 1 year in TRD patients achieving a response Numerous open-label studies have reported favorable outcomes with lithium augmentation in TRD. Thase and colleagues demonstrated its effectiveness in 20 non-responders to imipramine combined with psychotherapy. A subsequent study reported significant improvement in 13 out of 20 patients with major depressive disorder (MDD) resistant to desipramine. In the same year, Fontaine and colleagues confirmed the efficacy of lithium augmentation in 60 outpatients with MDD resistant

to desipramine or fluoxetine. An open-label dose-response study involving 11 sertraline-resistant MDD patients later found that most participants responded within one week, although response magnitude was not correlated with lithium plasma levels. Further studies supported lithium's effectiveness in venlafaxine-resistant depression, with one open-label trial reporting that 8 out of 22 outpatients responded, and another study showing that 38.5% of 13 venlafaxine-resistant MDD patients achieved a response following lithium augmentation. In contrast, two open-label studies conducted in elderly TRD patients (n = 13 and n = 21) failed to demonstrate significant improvement in depressive symptoms. However, a recent multicenter cohort study found that lithium augmentation was associated with greater clinical improvement in geriatric TRD patients compared to their non-geriatric counterparts. (Caldiroli et al., 2021) A number of head-to-head studies have evaluated the efficacy of lithium augmentation in treatment-resistant depression (TRD), providing insights into its relative performance against other therapeutic agents. An open-label trial involving 28 elderly TRD inpatients demonstrated higher response and remission rates in the lithium augmentation group compared to the phenelzine group. Two studies compared lithium augmentation with second-generation antipsychotics (SGAs). The first was an open-label study that randomized 20 TRD patients to either lithium or quetiapine augmentation. Both groups exhibited significant improvements in Hamilton Rating Scale for Depression (HAM-D) scores from baseline, with greater improvement observed in the quetiapine group during the first four weeks of augmentation. The second study, a randomized controlled trial (RCT) involving 30 TRD patients, reported no significant differences in clinical improvement between augmentation with lithium, olanzapine, or aripiprazole. Three studies compared lithium with anticonvulsant augmentation. In a randomized open-label study of 34 TRD patients, no significant differences in HAM-D scores were noted between lamotrigine and lithium groups at baseline or after eight weeks. Conversely, another open-label study of 88 TRD patients reported greater clinical improvement in the lamotrigine group by the second week, although no differences were evident by the study's endpoint. A third open-label study with 46 TRD inpatients found that lithium, but not carbamazepine, significantly enhanced the antidepressant effect of mirtazapine. The efficacy of lithium was also compared to triiodothyronine (T3) augmentation in two studies. Joffe and collaborators conducted an RCT involving 50 TCA-resistant patients, finding that both T3 and lithium were significantly more effective than placebo in reducing HAM-D scores. A subsequent observational study indicated higher remission rates with lithium sulfate augmentation alone compared to lithium sulfate combined with T3. (Caldiroli et al., 2021)

Two studies focusing on elderly populations have investigated the comparative efficacy of lithium augmentation and switching strategies in treatment-resistant depression (TRD). The first study, which included 65 participants, found comparable rates and speeds of response among patients receiving lithium, bupropion, or nortriptyline augmentation versus those switching to venlafaxine. In the second study, involving 32 participants, both lithium augmentation and switching to tricyclic antidepressants (TCAs) were identified as effective treatment strategies. In contrast, switching to phenelzine or initiating electroconvulsive therapy (ECT) demonstrated limited effectiveness. (Caldiroli et al., 2021) Lithium has demonstrated efficacy as an augmentation agent for treatment-resistant depression (TRD) in several controlled trials, though it is not FDA-approved for this indication. A study by Heninger et al. compared lithium augmentation (n = 8) with placebo augmentation (n = 7) in 15 patients who had failed at least one antidepressant. The lithium group showed a significant improvement in the global depression item of the Short Clinical Rating Scale (SCRS), with scores decreasing from 6.1 to 3.3 ($p < 0.012$), whereas the placebo group's scores increased from 5.6 to 5.8. Lithium demonstrated a rapid effect, with improvement observed within one week. Similarly, a double-blind study by Schöpf et al. involving 27 patients who had failed to respond to a tricyclic antidepressant (TCA) found that lithium augmentation (n = 14) significantly reduced Hamilton Depression Rating Scale (HAM-D) scores from 19.3 (SD = 4.9) to 10.4 (SD = 5.3) within one week ($p < 0.001$), while the placebo group (n = 13) showed minimal change. In another study, Katona et al. found that lithium (n = 29) was significantly more effective than placebo (n = 32) in patients who had not responded to fluoxetine or lofepramine. Response rates were 52% for the lithium group, compared to 25% for the placebo group ($X2 = 4.6$, $p < 0.05$). A study by Cappiello et al. reported that 28.6% of patients (n = 14) in the lithium augmentation group responded, compared to 0% in the placebo group (n = 15; $p < 0.042$). Conversely, Zusky et al. found no significant difference between 300 mg/day of lithium (n = 8) and placebo (n = 8) in treatment-resistant patients, suggesting that low-dose lithium may not be effective, potentially due to the small sample size. Stein et al. found that 750 mg/day of lithium was significantly more effective than placebo in a sample of 34 patients resistant to TCA treatment. The response rate for the 750 mg/day group was 44%, compared to 18% for the 250 mg/day lithium group ($X2 = 14.45$, $df = 1$, $p < 0.001$), and 22% for the placebo group. 250 mg/day was not effective for augmentation in this context. A study by Fava et al. compared the efficacy of fluoxetine (40–60 mg/day) alone (n = 15), fluoxetine (20 mg/day) with lithium augmentation (n = 14), and fluoxetine (20 mg/day) with desipramine (n = 12) in patients who had failed to respond to a 20 mg/day dose of fluoxetine. The response rates did not differ significantly

between groups: 29% for lithium plus fluoxetine, 25% for desipramine plus fluoxetine, and 53% for high-dose fluoxetine ($X2 = 2.9$, $df = 2$, $p = 0.24$). However, lithium plus fluoxetine and high-dose fluoxetine were significantly more effective than desipramine plus fluoxetine in terms of change in HAM-D score ($p = 0.04$). In a similar study by Fava et al. in 2002, there was no significant difference in response rates among the three treatment groups: lithium plus fluoxetine (23.5%), desipramine plus fluoxetine (29.4%), and high-dose fluoxetine (42.4%; $X2 = 2.9$, $p = 0.2$). A study by Nierenberg et al. found that lithium augmentation of nortriptyline ($n = 18$) was not more effective than placebo ($n = 17$) in a sample of 35 patients who had failed to respond to 1 to 5 antidepressants in the current episode. The response rate for the lithium group was 11.1%, compared to 17.6% for the placebo group, though this difference was not statistically significant. Lithium augmentation may have similar efficacy to second-generation antipsychotics (SGAs) for TRD. In a study by Yoshimura et al., lithium augmentation of paroxetine ($n = 10$) was compared with olanzapine ($n = 10$) and aripiprazole ($n = 10$) in patients who had failed paroxetine. The response rates were 40% for the lithium and aripiprazole groups, and 30% for the olanzapine group. The remission rates were 20%, 10%, and 20%, respectively. The change in HAM-D score was significant for all groups ($p < 0.001$), though the significance of the response and remission rates was not reported. Similarly, Bauer et al. Compared lithium augmentation ($n = 229$) to quetiapine augmentation ($n = 231$) and quetiapine monotherapy ($n = 228$) in a large sample of 688 patients with inadequate response to at least one antidepressant. The response rates were 46.2% for lithium, 52.4% for adjunctive quetiapine, and 50.7% for quetiapine monotherapy ($p = 0.6912$). Remission rates were 31.9%, 27.1%, and 23.6%, respectively ($p = 0.6496$). Common adverse events associated with lithium and SGA augmentation include tremors, headache, nausea and akathisia. (Ruberto et al., 2020)

Antiepileptic Drugs: Evidence regarding the efficacy of antiepileptic drugs (AEDs) as augmentation strategies in treatment-resistant depression (TRD) is mixed. In an initial double-blind randomized controlled trial (RCT) involving 23 TRD patients, lamotrigine did not significantly reduce scores on the Hamilton Depression Rating Scale (HAM-D) or Montgomery–Åsberg Depression Rating Scale (MADRS) compared to placebo. Similarly, a subsequent double-blind RCT with 34 TRD subjects showed no significant differences in outcomes between lamotrigine and placebo. Conversely, retrospective studies have indicated potential benefits of lamotrigine augmentation in TRD. In one study by Barbee and Jamhour, 48.4% of the 31 participants experienced marked improvement on the Clinical Global Impression (CGI) scale after 6 weeks of treatment, with no significant difference in lamotrigine dosage between responders and non-responders. Another retrospective study reported symptom

improvement in 76% of 25 TRD patients, and a third study involving 34 TRD patients noted early and statistically significant improvements in depressive symptoms such as mood, interest, cognitive function, irritability, and anergy, though sleep disturbances persisted. (Caldiroli et al., 2021) Lamotrigine has been investigated as an augmentation agent for treatment-resistant depression (TRD), though its efficacy remains controversial. Despite being studied in several trials, lamotrigine is not FDA-approved for this indication. A double-blind study by Santos et al. found no significant difference in response rates between lamotrigine (26.7%; n = 17) and placebo (35.7%; n = 17) in a sample of 34 participants who had failed two antidepressants (p = 0.6), with the small sample size potentially limiting the study's power. Similarly, a double-blind trial by Barbee et al. in 96 patients who had failed one antidepressant found no difference in response rates, with both groups achieving a 33% response rate (p = 0.956). In contrast, a study by Barbosa et al. observed a significant difference in response rates between lamotrigine (84.62%; n = 13) and placebo (30%; n = 10) in 23 patients who had failed one antidepressant (p = 0.013), although there was no significant difference in HAM-D or MADRS total scores. Another double-blind trial by Normann et al. also showed no significant difference in response rates between lamotrigine (55%) and placebo (50%) in a sample of 40 participants (p = NS). A study by Schindler et al. compared lamotrigine augmentation to lithium augmentation in a sample of 34 patients who had failed to respond to two antidepressants. The response rates were 53% for lamotrigine and 41% for lithium, while the remission rates were 23% and 18%, respectively. These results suggest that lamotrigine may be as effective as lithium for TRD. Adverse events associated with lamotrigine are generally mild and include nausea, rash, and dyspepsia.(Ruberto et al., 2020)

Phenytoin, evaluated in a small double-blind RCT of 20 major depressive disorder (MDD) patients resistant to selective serotonin reuptake inhibitors (SSRIs), showed no differences in response rates compared to placebo. Pregabalin, assessed in an open-label study involving 20 elderly TRD patients with comorbid generalized anxiety disorder, demonstrated significant reductions in depressive symptoms after 4 weeks of augmentation, with further improvements noted between weeks 8 and 12. Additionally, anxiety symptoms significantly improved. Similarly, an open-label study with 14 TRD patients showed that valproate augmentation led to sustained effectiveness over a 7-month period. Topiramate, previously shown to be beneficial in the depressive phase of bipolar disorder, was evaluated as an augmentation therapy for TRD in a double-blind RCT with 53 participants. Mowla and Kardeh reported that topiramate significantly reduced HAM-D scores compared to placebo, with notable improvements in symptoms such as depressed mood, insomnia, agitation, anxiety, and suicidality. Zonisamide,

considered for augmentation due to its partial pharmacodynamic overlap with lamotrigine and potential serotonergic effects, was preliminarily evaluated in TRD patients. Findings suggested that zonisamide may be a viable augmentation option for major depressive disorder (MDD) patients who do not respond to duloxetine. (Caldiroli et al., 2021)

A retrospective study evaluated the comparative efficacy of various augmentation strategies, including valproate, as add-on therapies to paroxetine in a cohort of 225 patients with treatment-resistant depression (TRD). The remission rates observed were 48.7% for valproate, 26.7% for risperidone, 32.6% for buspirone, 42.6% for trazodone, and 37.5% for thyroid hormone. However, the differences in remission rates across these adjunctive treatment groups were not statistically significant. (Caldiroli et al., 2021)

Ketamine is a non-competitive NMDA (N-methyl-D-aspartate) glutamate receptor antagonist primarily used as an anesthetic. It has been explored as an add-on treatment for treatment-resistant depression (TRD), with some small open-label studies showing significant reductions in depressive symptoms following intravenous (IV) ketamine administration. However, results from five double-blind randomized controlled trials (RCTs) have been mixed. In a study by Fava et al., IV ketamine doses of 0.5 and 1.0 mg/kg, but not lower doses (0.1 and 0.2 mg/kg), were superior to placebo in reducing the HAM-D6 score at 24 hours post-infusion, though no difference was observed at day 3. Conversely, a study by Ionescu et al. involving 26 TRD patients found that 0.5 mg/kg of IV ketamine did not outperform placebo in either short-term or long-term efficacy. Further analyses of Fava's study indicated no significant differences between men and women in treatment response. In a more recent analysis by Salloum et al., it was demonstrated that the time to relapse following a single IV ketamine infusion was dose-dependent. A significant reduction in suicidal ideation was observed at one month post-infusion, though not immediately after administration. (Caldiroli et al., 2021) Other recent studies have highlighted the antidepressant effects of ketamine. In a study by Berman et al., ketamine ($n = 7$) produced greater reductions in HAM-D scores compared to saline ($n = 7$), although the difference in response rates (50% for ketamine vs. 12.5% for placebo) was not statistically significant ($p > 0.05$). However, a significant condition-by-time effect on HAM-D scores was observed ($F = 3.97$, $df = 5, 30$; $p = 0.02$). Zarate et al. conducted a study with ketamine monotherapy ($n = 17$), which demonstrated significantly better efficacy than placebo ($n = 14$) in patients who had failed at least two previous antidepressants ($F1,203 = 58.24$; $p < 0.001$). 71% of participants receiving ketamine responded, compared to 0% in the placebo group. 29% of the ketamine group achieved remission, while no participants in the placebo group remitted. The statistical significance of these results was not specified. Murrough et al. replicated similar

findings in a sample of patients who had failed at least three antidepressants. In this study, the ketamine group (n = 47) had a significantly higher response rate (64%) compared to the active placebo group, which received midazolam (n = 25; 28%; $p < 0.006$). At 24 hours post-treatment, the average MADRS score in the ketamine group was 14.77 (95% CI, 11.73 – 17.80), compared to 22.72 in the placebo group (95% CI, 18.85–26.59; $t = 3.34$, $df = 68$, $p < 0.001$).(Ruberto et al., 2020) A double-blind study by Ionescu et al. found no significant difference in the efficacy of ketamine (n = 13) versus saline placebo (n = 13) in 26 patients who had previously failed at least five antidepressants. The response rates were 25% for ketamine and 33% for placebo ($p > 0.05$), while remission rates were 17% and 8%, respectively ($p > 0.05$). Notably, 50% of participants had previously failed electroconvulsive therapy (ECT), which may have contributed to the lack of significant results due to the high severity of treatment resistance. In articles used in source (Ruberto et al., 2020) ketamine has been studied in doses ranging from 0.2 to 1 mg/kg, with 0.5 mg/kg being the most commonly used. In a study by Su et al., 0.2 mg/kg (n = 23) and 0.5 mg/kg (n = 24) doses were compared to saline (n = 24) in 71 participants who had failed more than two antidepressants. Although the 0.5 mg/kg dose showed a higher response rate (45.8% vs. 39.1% for the 0.2 mg/kg group), the difference between the two ketamine groups was not statistically significant ($p = 0.77$). In contrast, Fava et al. found that both 0.5 mg/kg and 1.0 mg/kg doses were significantly more effective than the active placebo, midazolam, in a sample of 99 patients who had failed at least two antidepressants ($p < 0.0001$). Response rates were 59%, 53%, and 11% for the 0.5 mg/kg, 1.0 mg/kg, and midazolam groups, respectively ($p = 0.04224$). Lenze et al. tested a 96-hour ketamine infusion at 0.6 mg/kg (n = 10) versus a 40-minute infusion at 0.5 mg/kg (n = 10) in 20 patients who failed two antidepressants. The response rates were 40% and 20%, respectively, but the difference was not statistically significant. Domany et al. investigated oral ketamine in 41 patients who had failed at least two antidepressants. The response rate was significantly higher in the ketamine group (31.8%) compared to the placebo group (5.6%; $X^2(1) = 4.27$, $p < 0.05$), with remission rates of 27.3% versus 0%, respectively ($X^2(1) = 5.78$, $p < 0.05$). A double-blind crossover study by Lapidus et al. compared intranasal ketamine with a placebo in 20 patients who had failed at least one antidepressant. The ketamine group showed a significant improvement in depression symptoms 24 hours after treatment ($t = 4.39$; $p < 0.001$), with a response rate of 44% compared to 6% in the placebo group ($p = 0.033$). Adverse events associated with ketamine include headaches, drowsiness, nausea, abnormal sensations, and acute dissociation during or immediately after treatment. Ketamine can also lower blood pressure, but these side effects are

typically mild and temporary. While ketamine produces rapid antidepressant effects, these effects may not be sustained. (Ruberto et al., 2020)

The nasal-spray formulation of esketamine, the S-enantiomer of ketamine, has been approved by the FDA and European Medicines Agency (EMA) as an adjunctive treatment for TRD. Two double-blind RCTs supported its short-term efficacy, showing that esketamine was superior to placebo for augmenting antidepressant (AD) treatment in TRD over a 4-week period. However, one study by Fedgchin et al. found no significant difference when esketamine was administered at 84 mg twice weekly. In contrast, a study by Daly et al. demonstrated that esketamine was superior to placebo in preventing relapse in 297 TRD patients who had achieved stable response or remission after 16 weeks of esketamine as an add-on to their existing AD therapy. More recently, Ochs-Ross et al. reported no differences between esketamine and placebo in reducing MADRS scores in elderly TRD patients, although a significant reduction was noted in those aged 65–74 years, but not in those aged ≥ 75 years. Encouraging long-term results were also found in a study by Wajs et al., showing sustained improvements in depressive symptoms following esketamine augmentation. (Caldiroli et al., 2021) In a placebo-controlled study by Singh et al. intravenous esketamine was compared at doses of 0.2 mg/kg (n = 9) and 0.4 mg/kg (n = 11) to placebo (n = 10) in 30 patients who had failed one antidepressant. Response rates were 67% (p = 0.013) and 64% (p = 0.014) for the 0.2 mg/kg and 0.4 mg/kg doses, respectively, compared to 0% in the placebo group. The least squares mean changes from baseline to endpoint were −16.8 (SE = 3.00) for 0.2 mg/kg and −16.9 (SE = 2.61) for 0.4 mg/kg. Popova et al. found that intranasal esketamine significantly reduced MADRS scores in 39 patients who had failed at least one antidepressant. Response rates for esketamine (69.3%) and placebo (52%) were significantly different (odds ratio = 2.4, 95% CI = 1.30, 4.54), and remission rates were 52.5% versus 31.0%. However, it is unclear if these results were statistically significant. Fedgchin et al. found that 84 mg esketamine did not significantly reduce MADRS scores compared to placebo (p = 0.088), but the 56 mg dose showed a significant reduction (−4.1; [−7.76, −0.49], p = 0.027). Daly et al. reported a dose-response relationship with esketamine, where higher doses were more effective than lower doses, with all doses significantly outperforming placebo (p < 0.05). The most frequent adverse effects of intranasal esketamine include nausea, dizziness, and dissociation. One of the challenges with intranasal ketamine is variability in absorption among individuals, which can complicate administration. In a study by Gálvez et al., participants experienced difficulty self-administering all 10 sprays due to side effects like lack of coordination. For greater dosing accuracy and ease of administration intravenous delivery is generally preferred. (Ruberto et al., 2020)

Psychostimulants:

Fenfluramine, a sympathomimetic amine that activates serotoninergic pathways in the brain, was investigated by Price and colleagues in a study of 15 patients with treatment-resistant depression (TRD). The results showed no statistically significant evidence of either transient or sustained clinical improvement during the 2-week period of fenfluramine augmentation with desipramine.

Lisdexamfetamine Dimesylate: In a study by Richards and co-authors, the results of two multicenter, double-blind randomized controlled trials (RCTs) involving 826 patients with TRD were presented. The data indicated that lisdexamfetamine dimesylate did not provide any significant benefits compared to a placebo in these patients.

Methylphenidate: Methylphenidate (MPH), a central nervous system stimulant, has been explored as a potential augmentation therapy for patients with refractory depression. However, preliminary results are not promising. In an initial double-blind RCT, no statistically significant differences were found between extended-release MPH and placebo in 50 patients with TRD. Similarly, another double-blind RCT reported no significant differences in the MADRS total scores between osmotic-release oral system MPH and placebo at the study endpoint. However, MPH did show superiority over placebo in improving symptoms of apathy and fatigue, as measured by the multidimensional assessment of fatigue (MAF) scale and the apathy evaluation scale (AES).

Modafinil: A retrospective chart review conducted by Nasr on 78 TRD outpatients found preliminary but promising results for modafinil, a wake-promoting agent, as an augmentation therapy. Among the patients, 11 achieved remission, and many others showed improvement in depressive symptoms, particularly with respect to sleepiness, fatigue, and anergy. (Caldiroli et al., 2021)

Non-Psychopharmacological Agents:

Acetylsalicylic Acid (ASA): A study by Mendlewicz et al. found that acetylsalicylic acid (ASA) augmentation to selective serotonin reuptake inhibitors (SSRIs) significantly reduced HAM-D total scores in a cohort of 17 patients with treatment-resistant depression (TRD). The response rate was 52.4%, with a remission rate of 43%. Notably, 82% of those who responded to treatment achieved remission.

Metyrapone, a cortisol synthesis inhibitor, was evaluated in a double-blind randomized controlled trial (RCT) involving 165 patients. The results indicated no significant improvement in depressive symptoms compared to the placebo.

Minocycline: An open-label pilot trial conducted by Avari and colleagues assessed minocycline augmentation in a small sample of older adults with TRD over an 8-week period. The remission rate in this study was 31%. Subsequently, a double-blind RCT involving 39 patients with TRD investigated minocycline (200 mg/day) as an adjunctive treatment to antidepressants. While the study did not demonstrate significant superiority of minocycline over placebo in reducing HAM-D scores at week 4, a subgroup analysis revealed a significant difference when patients were stratified by baseline C-reactive protein (CRP) plasma levels. Patients with elevated CRP (≥3 mg/L) receiving minocycline showed greater improvement in depressive symptoms compared to all other groups. (Caldiroli et al., 2021)

Pindolol: Two double-blind randomized controlled trials (RCTs) investigated pindolol augmentation in small cohorts of patients with treatment-resistant depression (TRD), with sample sizes of 10 and 9 participants, respectively. The first trial, conducted by Moreno et al., found no statistically significant difference between pindolol and placebo in improving depressive symptoms. Conversely, the second trial demonstrated significant improvement in HAM-D scores when pindolol was administered as a single high dose (7.5 mg) compared to the same total dose divided into 2.5 mg three times daily (t.i.d.), suggesting the high-dose regimen may be more effective in SSRI-refractory patients. However, two larger double-blind RCTs failed to confirm pindolol's efficacy as an adjunctive treatment for TRD. A study by Perez et al., involving 80 outpatients, showed no significant differences in HAM-D scores or remission rates between patients receiving pindolol (2.5 mg t.i.d.) and placebo. Similarly, Perry and colleagues used a hemi-crossover design and reported no significant differences in antidepressant response when pindolol was added to SSRI monotherapy compared to placebo.

Reserpine: Price et al. examined the effect of reserpine augmentation in eight patients with melancholic depression receiving desipramine. Only one patient achieved rapid resolution of depressive and psychotic symptoms within 48 hours; however, the response was short-lived, with relapse occurring within two weeks. Overall, no significant improvement in depressive symptoms was observed in the cohort.

Testosterone: Miller et al. conducted an open-label pilot study on nine women with TRD, evaluating low-dose transdermal testosterone. The results showed a statistically significant reduction in MADRS scores beginning at week 2, sustained over the 8-week follow-up period. Two-thirds of the participants responded to treatment, and one-third achieved remission. In contrast, a recent double-blind RCT involving 101 women failed to demonstrate significant superiority of low-dose testosterone over placebo after 8 weeks of treatment in alleviating depressive symptoms, fatigue, or sexual dysfunction. (Caldiroli et al., 2021)

T3/T4: Rudas and colleagues conducted an open-label study involving nine patients with treatment-resistant depression (TRD). The findings revealed a significant reduction in HAM-D total scores, with four participants demonstrating a favorable response to high-dose T4 therapy. Thyroid hormones, T3 and T4, have been studied extensively over the years for their potential role as augmentation strategies in treatment-resistant depression (TRD). Although T3 has not received FDA approval, it has shown comparable efficacy to other augmentation agents for depression. As part of the STAR*D study, Nierenberg et al. compared the efficacy of T3 (n = 73) with lithium (n = 69) in participants who had failed to respond to at least two antidepressants. Response rates were 23.3% for the T3 group and 16.2% for the lithium group ($X^2 = 1.70$, df = 1, p = 0.1918), while remission rates were 24.7% and 15.9%, respectively ($X^2 = 0.63$, df = 1, p = 0.4258). Although these differences were not statistically significant, T3 was associated with significantly fewer adverse events compared to lithium (p = 0.045). Similarly, Joffe et al. reported comparable results in a study of 50 patients who had failed to respond to a tricyclic antidepressant (TCA). Among the 17 patients receiving T3, 41.2% responded to treatment, compared to 35.3% in the lithium group and 12.5% in the placebo group (p = 0.058 for T3 vs. placebo, p = 0.098 for lithium vs. placebo). While response rates did not reach statistical significance, changes in HAM-D scores did. The mean HAM-D score at endpoint was 14.9 (SD = 8.0) in the placebo group, 11.0 (SD = 6.4) in the T3 group (F = 4.86, df = 1, 32, p = 0.035), and 12.1 (SD = 7.3) in the lithium group (F = 7.62, df = 1, 32, p = 0.01). In another study by Joffe et al., T3 (n = 10), lithium (n = 9), and their combination (n = 9) were compared to placebo (n = 8) in patients who had failed one antidepressant. No significant differences in HAM-D score changes were observed among the groups (F = 0.551, df = 3, p = 0.651). Symptomatic improvement was noted as early as two weeks. Joffe and colleagues also investigated whether T3 (n = 17) was more effective than L-thyroxine (T4; n = 21) in 38 participants who had not responded to a TCA. Results indicated that T3 was significantly more effective, with response rates of 52.9% for T3 compared to 19.0% for T4 (p = 0.026). Participants in the T3 group had significantly lower HAM-D scores at endpoint (12.6; SD = 6.2) compared to the T4 group (16.6; SD = 6.3; $p < 0.05$). In a broader comparison, Fang et al. evaluated the efficacy of thyroid hormones (n = 48) against other augmentation agents, including risperidone (n = 45), valproate (n = 39), buspirone (n = 46), and trazodone (n = 47), in a sample of 225 participants who had failed at least one antidepressant. No significant differences were found in efficacy or adverse event rates across groups. Response rates were 58.3% (thyroid hormones), 46.7% (risperidone), 61.5% (valproate), 56.5% (buspirone), and 61.7% (trazodone) ($F/X^2 = 2.748$, p = 0.601). Remission rates were 26.7%, 48.7%, 32.6%, 42.6%, and 37.5%, respectively ($F/X^2 = 5.336$, p

= 0.255). Some studies have raised questions about the efficacy of T3. Appelhof et al. conducted a double-blind trial comparing T3 at 25 μg/day (n = 30), T3 at 50 μg/day (n = 30), and placebo (n = 53). Response rates were 46% across all groups ($X^2 = 0.002$, p = 0.99), with remission rates of 36% in the placebo group and 32% in both T3 groups ($X^2 = 0.175$, df = 2, p = 0.92). When T3 groups were combined and compared to placebo, the response rate difference was 0.004 (95% CI: −0.187 to 0.195). Gitlin et al. also found no significant effects of T3 compared to placebo on depressive symptoms in 16 patients who had failed to respond to imipramine (F = 2.68, df = 1, p = 0.12). T3 is generally well-tolerated, but some patients may experience palpitations, nervousness, sweating, and tremors. It is contraindicated in individuals with hyperthyroidism. (Ruberto et al., 2020)

Anti-Parkinson/Dementia Agents: An open-label study evaluating pramipexole as an augmentation therapy reported a significant reduction in psychometric scores in 12 patients with treatment-resistant depression (TRD). Similarly, Cassano et al. conducted a prospective open trial in which ropinirole was added to either tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) in seven TRD patients, showing a significant decrease in the MADRS total scores at the study endpoint.

Naltrexone: A pilot double-blind randomized controlled trial (RCT) evaluated low-dose naltrexone (LDN, 1 mg twice daily) versus placebo as an augmentation strategy in 12 TRD patients. Results indicated no significant improvement in the primary outcomes, including HAM-D and CGI scores, for the LDN group compared to placebo. However, a secondary outcome measure, the MADRS scores, demonstrated a statistically significant improvement in the LDN group (Mischoulon et al., 2017).

S-adenosyl Methionine (SAMe): De Berardis et al. conducted an open-label, single-blind study involving 33 patients classified as Stage II TRD under the Thase and Rush classification. SAMe was added to the patients' existing treatment regimens, resulting in a significant reduction in HAM-D total scores. In contrast, a double-blind RCT by Targum et al. involving 234 TRD patients found no statistically significant differences in depressive symptom improvement between the SAMe and placebo groups.

Supplements: Siwek et al., in a double-blind RCT, investigated the impact of adjunctive zinc therapy in 21 patients resistant to imipramine treatment. Their findings demonstrated a significant reduction in depressive symptoms in the zinc group compared to the placebo group. (Caldiroli et al., 2021)

Discussion:

New evidence continually emerges comparing the effectiveness of various therapies for treatment-resistant depression. Different approaches are employed, such as dose optimization of the current medication, switching to a different pharmacological class of substance, or adding an augmentation agent. However, the heterogeneity of the clinical presentation of this disorder complicates the selection of the most effective strategy. The existing conclusions are limited, fragmented, and inconclusive. Nevertheless, evidence-based considerations regarding the effectiveness of adjunctive medications in adult patients with TRD should be taken into account. (Caldiroli et al., 2021) The analysis of studies indicates that several pharmacological agents can serve as effective adjunctive treatments for treatment-resistant depression (TRD). It has been demonstrated that T3, nortriptyline, aripiprazole, brexpiprazole, lithium, quetiapine, modafinil, olanzapine (combined with fluoxetine), and lisdexamfetamine exhibit greater efficacy compared to placebo. Regarding cases of treatment discontinuation for any reason, significant differences were observed for ziprasidone and mirtazapine when compared to placebo. (Nuñez et al., 2022) It is important to note that combination therapy may lead to the accumulation of side effects and complicate adherence to therapeutic recommendations. (Caldiroli et al., 2021) Moreover, in one of the articles (JAMA Psychiatry, Freeman, 2020) addresses the issue of limited knowledge regarding the maintenance of remission in treatment-resistant depression. He emphasizes the importance of an individualized approach for each patient and recommends continuing the therapy that successfully resolved the patient's most recent depressive episode.
Evidence suggests that second-generation antipsychotics represent a viable first-line strategy for adjunctive treatment in the pharmacological management of treatment-resistant depression. The exact mechanism of action of second-generation antipsychotics in augmentation is not fully understood; however, it is assumed that SGAs may exhibit activity as 5-HT2A receptor antagonists, alpha-2 adrenergic receptor antagonists, 5-HT1A receptor agonists, and monoamine reuptake inhibitors. The literature robustly supports the efficacy of aripiprazole and quetiapine, with additional data indicating favorable outcomes from the combination of olanzapine with fluoxetine, as well as the use of risperidone. Aripiprazole, as an augmentation agent (mean dose 10.68 ± 3.1 mg/day), demonstrates significant efficacy and low discontinuation rates. Subsequent studies indicate that aripiprazole is more effective than placebo in alleviating depressive symptoms in patients with treatment-resistant depression, both at fixed and variable doses (ranging from low to moderate). Additionally, it was found that moderate doses (12 mg/day) are more effective than low doses (3 mg/day). Similarly, quetiapine (mean dose 156.74 ± 97.6 mg/day) showed significant benefits in both treatment response and remission rates compared to placebo. Likewise, olanzapine as an augmentation to SSRIs (mean

dose 8.5 ± 3.9 mg/day) leads to higher remission rates compared to placebo or SSRIs in monotherapy. Quetiapine and olanzapine have shown promising effects, although, the clinical trials are still too limited to draw definitive and conclusive conclusions. However this approach seems to be essential for addressing treatment resistance. (Nuñez et al., 2022; Caldiroli et al., 2021) Risperidone demonstrated greater efficacy in alleviating acute depressive symptoms and preventing disease relapses compared to placebo, and thus it may be considered in clinical practice as an adjunctive treatment. In contrast, despite its favorable side effect profile, ziprasidone is not recommended for augmentation in the treatment of TRD, as previous studies have shown mixed results, and the data are too limited to draw definitive conclusions. (Caldiroli et al., 2021) Promising evidence supports the use of brexpiprazole and cariprazine, both classified as second-generation antipsychotics. Brexpiprazole, administered as an adjunctive treatment, demonstrated a significant reduction in depressive symptom severity compared to placebo following six weeks of therapy. It has received FDA approval as an augmentation agent for the management of treatment-resistant depression. Conversely, cariprazine, although not yet approved by the FDA for this indication, has shown a significant decrease in MADRS scores compared to placebo after eight weeks of treatment. Further long-term studies are warranted to evaluate the efficacy and safety of brexpiprazole and cariprazine in treatment-resistant depression. (Nuñez et al., 2022) It is important to acknowledge, however, that certain second-generation antipsychotic medications, particularly olanzapine, may induce significant metabolic changes. (Ruberto et al., 2020)

In many clinical studies investigating mood stabilizers (lithium and lamotrigine) in patients with treatment-resistant depression, lithium has been shown to exhibit superior efficacy compared to placebo. Lithium, as an add-on treatment for treatment-resistant depression, is one of the most established and extensively researched substances. According to (Nuñez et al., 2022) when administered over a duration of 1 to 12 weeks at doses ranging from 300 to 1200 mg/day, lithium serves as an effective adjunct to tricyclic antidepressants, selective serotonin reuptake inhibitors, or other antidepressant therapies. Research suggests a rapid onset of lithium's therapeutic effects in the treatment of depression, irrespective of dosage or treatment duration. In studies with a duration of up to 3 weeks, lithium demonstrated a significantly higher response rate compared to placeb. However, no significant differences were observed between lithium and placebo in remission rates. Conversely, according to source (Caldiroli et al., 2021), studies show conflicting results regarding the effectiveness of lithium as an add-on treatment for TRD. According to the study (Ruberto et al., 2020), lithium demonstrates greater efficacy than augmenting TCA with another antidepressant, while showing comparable effectiveness to

adding second-generation antipsychotics to TRD therapy. However, considering the overall literature, it appears that lithium holds potential in this context. It is important to note that the numerous drug interactions and potential toxicity of lithium require regular monitoring of its plasma concentration. (Nuñez et al., 2022; Caldiroli et al., 2021) Studies suggest that lamotrigine, administered at doses of 100-400 mg/day, demonstrates limited efficacy compared to placebo. This outcome may be influenced by inconsistencies in trial design, variations in dosing, the short treatment duration (up to 4 weeks), and an unexpectedly high placebo response rate. (Nuñez et al., 2022)

The use of thyroid hormones in the treatment of affective disorders has elicited mixed opinions. There is evidence suggesting that these substances may be an effective adjunct in the management of treatment-resistant depression (TRD), as they may accelerate the action of antidepressants, particularly in women. The data, however, are inconsistent. Some studies indicate a significant advantage of T3 in treatment efficacy compared to placebo and lithium. Nevertheless, certain post-hoc analyses of short-term studies (lasting less than three weeks) have not shown a significant difference in response rates between T3 and placebo. The discrepancies in results may stem from inconsistencies in the design of various analyses, heterogeneity among studied populations, the absence of a standardized definition of TRD, and variations in the administered doses of T3. (Nuñez et al., 2022) According to study (Caldiroli et al., 2021), the choice of T3/T4 as an adjunctive treatment for depression is not currently recommended.

Emerging evidence indicates that impairments in the glutamatergic signaling pathway within the brain may play a critical role in the pathophysiology of major depressive disorder (MDD). Clinical studies have demonstrated that the intravenous administration of ketamine at a sub-anesthetic dose (0.5 mg/kg body weight) can elicit a rapid antidepressant response and significantly reduce suicidal ideation in affected patients. While research on this application of ketamine is promising, there remains a lack of data regarding the long-term durability of its quick therapeutic effects. Furthermore, the use of ketamine has been associated with several adverse events, and its intravenous mode of administration presents challenges for routine implementation in clinical practice. Esketamine, the S-enantiomer of ketamine, demonstrates approximately four times higher affinity for the glutamate receptor than ketamine, enabling its use at significantly lower doses and reducing the likelihood of dose-dependent dissociative side effects associated with ketamine. Its administration is more convenient as it is available in a nasal spray formulation; however, self-administration by patients at home is currently not feasible, limiting its application in routine clinical practice. The FDA has approved intranasal

esketamine for use as an augmentation therapy in treatment-resistant depression (TRD). Nonetheless, most research has primarily examined its short-term effects, typically within the initial 4-week treatment period, leaving its long-term clinical value uncertain and highlighting the need for additional studies. While prolonged esketamine treatment may help prevent relapses of depressive episodes, evidence regarding its sustained antidepressant and anti-suicidal effects is inconsistent. In study (McIntyre et al., 2021), suicide attempts were observed in patients after the discontinuation of esketamine therapy. Given that TRD is a chronic disorder with challenges in achieving stable remission and a high risk of suicide, it remains unclear whether esketamine should be continued after the acute phase, for what duration, at what dosage, and in which patient populations. The appropriate method for discontinuing the drug also warrants consideration. Furthermore, the potential for misuse and the impact of long-term use on cognitive functions must be carefully assessed. Further controlled studies are essential to better understand the long-term efficacy and safety profile of esketamine. (Caldiroli et al., 2021) Although S-ketamine is considered a relatively safe drug, psychiatric, cardiovascular, and neurological side effects have been reported during its use. Therefore, it is essential to investigate its safety in long-term application. (Borbély et al., 2022) In addition to the efficacy of the substances under investigation, it is essential to consider the individual profile of benefits and side effects associated with each, including tolerability and the time required to observe therapeutic effects. It is therefore important to determine which factors should take precedence for each patient. For instance, among patients at high risk of suicide, the priority may be to achieve a rapid therapeutic response, even at the cost of tolerability—provided that the side effects are not severe. For example, for patients at acute suicidal risk, particularly, the use of ketamine and esketamine should be considered, given the available evidence suggesting a rapid onset of action and efficacy in addressing suicidal ideation. (Ruberto et al., 2020)

Research has also been initiated on the potential antidepressant effects of amantadine, suggesting that it may be a viable option for the treatment of treatment-resistant depression (TRD). However, there is still insufficient data to draw definitive conclusions. Amantadine may share similarities with ketamine, as both are NMDA receptor antagonists, but due to its oral administration, amantadine could offer easier integration into daily clinical practice. Further studies are needed to assess the efficacy of amantadine as an augmentation treatment for TRD. (Ruberto et al., 2020)

Currently, there is growing interest in the use of psychedelic substances containing tryptamine derivatives (e.g., psilocybin) in the treatment of TRD. Research on psilocybin has shown promising results, especially when used as an adjunct to regular psychotherapy. There are

theories suggesting that these compounds affect the serotonergic/monoaminergic systems, but further details, such as optimal dosages and treatment regimens, require additional research and thorough investigation. These drugs may represent a potential future alternative approach in the treatment of treatment-resistant depression. (Borbély et al., 2022)

The study provides data indicating that modafinil and lisdexamfetamine, as augmentation agents, may alleviate depressive symptoms. However, this effect pertains to the treatment response rate rather than the remission rate. Guidelines, such as those from CANMAT, recommend caution when using stimulant and stimulant-like molecules for this indication. (Nuñez et al., 2022) Caution in choosing these medications is particularly important, especially since study (Caldiroli et al., 2021) questions their effectiveness based on the evidence available so far.

The evidence for the effectiveness of augmenting an antidepressant (AD) with another antidepressant (AD) is limited, and the use of add-on therapy with antiepileptic drugs, pramipexole, ropinirole, ASA, metyrapone, reserpine, testosterone, naltrexone, SAMe, amphetamines, or zinc is not supported by the available evidence. (Caldiroli et al., 2021)

Many of the studies considered in the meta-analysis had limited sample sizes (e.g., those focusing on thyroid hormones, nortriptyline, lithium, and stimulants) and short durations of follow-up. Additionally, it should be noted that older studies (e.g., involving thyroid hormones and lithium) may have reported side effects and dosing less accurately due to the design methodologies prevalent at the time. These issues could have led to broader confidence intervals and increased variability in outcomes. Moreover, variations in clinical trial standards in the past might have affected the reporting of adverse events and measures of efficacy. There is also the possibility that some of the observed results in these studies were influenced, at least in part, by the natural progression of the illness. (Nuñez et al., 2022) Furthermore, it should be noted that the studies analyzed in the publications display considerable heterogeneity with regard to factors such as duration, dosage, patient setting (hospitalized vs. outpatient), and the type of primary medication used. (Nuñez et al., 2022; Caldiroli et al., 2021) Akso it is important to note that the studies analyzed were based on different scales, such as MADRS, HAM-D, QIDS-SR, CGI-I, and BDI-II, which may complicate the comparison of results between them. A significant limitation in research on treatment-resistant depression is the absence of a standardized definition of the condition. The number of antidepressant treatments required to define depression as "treatment-resistant" can vary from one to eight, creating challenges in comparing the efficacy of different therapies. This variability arises from the fact that some studies may include participants who are more resistant to treatment than those in other studies.

The file drawer effect could also influence the conclusions, as it suggests that studies with insignificant results are less likely to be published. As a result, we may have limited insight into the number of randomized controlled trials (RCTs) that yielded non-significant findings for these drugs. Without this data, it becomes difficult to accurately determine which medications are truly the most effective. (Ruberto et al., 2020)

Electroconvulsive Therapy (ECT) has demonstrated exceptional efficacy in the treatment of various neuropsychiatric disorders, including major depressive disorder (MDD). However, further research is essential to elucidate the underlying neurobiological mechanisms through which ECT exerts its effects. Such insights would facilitate the optimization of stimulation parameters, the identification of reliable biomarkers of therapeutic response, and the development of targeted, safe, and effective treatment protocols. Emerging evidence indicates that ECT induces changes across multiple brain regions, yet our understanding of how to strategically determine electrode placement and stimulation parameters to maximize clinical outcomes remains in its infancy. Research suggests that alterations in brain activity and connectivity, particularly within the frontal lobe and neural networks involved in emotion regulation and executive function, may underlie the therapeutic effects of ECT and help predict treatment efficacy. For instance, the connectivity between the dorsal prefrontal cortex and the limbic and default-mode networks has been identified as a significant predictor of response to ECT. It remains uncertain whether the optimization of ECT for maximal antidepressant efficacy is best achieved through fMRI-guided electrode placement or through current-amplitude-titrated or electric-field-informed dosing based on hippocampal alterations. Moreover, it is crucial to disentangle the direct effects of the electrical stimulus from the therapeutic role of the induced seizure. One of the most concerning potential side effects of ECT is impairment of episodic and autobiographical memory. The hippocampus and amygdala, key structures involved in these memory processes, are also very important to the therapeutic mechanisms of ECT. However, the connection between the stimulation of these regions and the possibility of associated memory dysfunction remains poorly understood. Alongside investigating the underlying mechanisms, it is crucial to explore strategies aimed at mitigating these side effects to enhance the overall efficacy and safety of the treatment. Additionally, there may be inflammatory and/or hormonal profiles in some patients that serve as relative indications or contraindications for ECT. While a comprehensive and unified understanding of the mechanisms underlying ECT and its effects on various psychiatric disorders, ranging from mood disorders to catatonia, remains elusive, existing evidence suggests that ECT modulates dysregulated neurocircuitry in pathological states through the repeated application of electric

fields and/or seizure activity. This likely facilitates the restoration of disrupted neurocircuit activity across multiple biological levels (e.g., molecular, cellular, anatomical, physiological), leading to more adaptive circuit dynamics and, ultimately, the achievement of euthymia. (Kritzer et al., 2023) Moreover, while there are guidelines on sustaining response or remission in MDD with effective treatment, knowledge about maintaining remission in treatment-resistant depression (TRD) remains limited, apart from continuation strategies involving ECT. (Voineskos et al., 2020)

Research indicates that individuals with depression exhibit reduced levels of physical activity and are more prone to a sedentary lifestyle compared to the general population. Considering the well-documented health benefits of high physical fitness, it is imperative to implement targeted support and motivational strategies to assist those facing challenges in adopting a more active lifestyle. Depressive symptoms often hinder the initiation and maintenance of regular physical activity; however, effective treatment and symptom alleviation can play a pivotal role in enhancing activity levels in this population. (Griffiths et al., 2022) Healthy lifestyle and regular physical activity significantly contribute to enhancing mood and overall well-being. Fitness techniques, defined as a form of physical culture that incorporates general developmental exercises performed in harmony with rhythmic music, can serve as an effective method of physical rehabilitation. These techniques are particularly beneficial for individuals experiencing psychological trauma and for patients with varying levels of physical fitness who are managing mental health disorders. Rehabilitation fitness is a relatively new concept that focuses on functional recovery through targeted strength exercises, aiming to improve both the physical and mental health of individuals, regardless of age or the presence of comorbid conditions. (Rybalko et al., 2024; Souza et al., 2023) Yoga also can be considered a form of physical and psychological rehabilitation, primarily due to its mental component. Research has demonstrated that the practice of yoga significantly reduces symptoms of anxiety and depression, highlighting its multifaceted impact on overall health. (Lewandowska et al., 2018)

Study 21 examined the impact of incorporating mindfulness-based cognitive therapy (MBCT) into standard antidepressant treatment on the severity of depressive symptoms. Mindfulness-based cognitive therapy is a two-month group training program that combines mindfulness meditation techniques with elements of cognitive-behavioral therapy. The goal of MBCT is to teach participants to recognize and interrupt maladaptive automatic cognitive patterns and to cultivate a nonjudgmental and compassionate attitude toward their own thoughts and feelings. This therapy is effective for patients with current depressive symptoms as well as those in remission. However, contrary to expectations, the study did not demonstrate a significant

reduction in depressive symptoms in patients with TRD, when MBCT was used alongside conventional treatments compared to standard therapy alone. Nevertheless, the study found significantly higher remission rates, lower levels of rumination, and improved subjective quality of life in the experimental group (MBCT + treatment as usual). (Cladder-Micus et al., 2018)

Conclusions:

The management of treatment-resistant depression (TRD) represents a significant challenge in contemporary psychiatry. Given the limited efficacy of standard therapeutic approaches, especially in patients with severe manifestations of the disorder, numerous pharmacological strategies have been investigated as potential adjunctive treatments. Among these, particular attention has been directed toward atypical antipsychotics, lithium, thyroid hormones, ketamine, and various experimental therapies. Atypical antipsychotics, including aripiprazole, brexpiprazole, quetiapine, and olanzapine, have demonstrated efficacy as adjunctive therapies to conventional antidepressants. Aripiprazole, supported by the most robust clinical evidence, is relatively well-tolerated. Brexpiprazole, while less extensively studied, also appears effective, particularly in alleviating symptoms of TRD. Quetiapine and olanzapine offer additional therapeutic value, especially in severe cases. In contrast, ziprasidone and cariprazine, despite their potential benefits, are associated with a higher incidence of adverse effects, thereby limiting their clinical utilit. Lithium, a well-established mood stabilizer, remains one of the most effective augmentation agents for TRD. Its efficacy has been substantiated both as an adjunctive treatment and as monotherapy. However, its long-term use is constrained by potential toxicity and adverse effects, which often preclude its adoption as a first-line intervention. Thyroid hormones, particularly triiodothyronine (T3) and thyroxine (T4), have also demonstrated utility in TRD management. T3, in particular, has shown efficacy, especially in patients with coexisting hypothyroid symptoms, whereas the therapeutic role of T4 requires further empirical validation. Ketamine and its derivative, esketamine, represent innovative therapeutic agents targeting glutamatergic pathways. Esketamine, approved by the FDA for intranasal administration, offers rapid therapeutic effects, particularly in individuals refractory to other interventions. Ketamine, though similarly effective, necessitates additional research to elucidate its long-term safety and clinical efficacy. Other adjunctive treatments, such as lamotrigine, mirtazapine, bupropion, and tricyclic antidepressants (TCAs), have also been employed in TRD. Lamotrigine, despite being primarily classified as an anticonvulsant, exhibits potential in mitigating TRD symptoms. Mirtazapine and bupropion have demonstrated effectiveness when combined with SSRIs or SNRIs, particularly in cases of atypical depression. TCAs, while

efficacious, are associated with a higher burden of adverse effects, thereby restricting their application in clinical practice.

The treatment of TRD necessitates a measured and individualized approach. Careful consideration of the risk-benefit profile of each intervention is essential, particularly given the potential for adverse effects associated with agents such as lithium or atypical antipsychotics. The development of standardized definitions for TRD would facilitate more rigorous clinical research and enable meaningful comparisons across studies. Furthermore, advancements in identifying biomarkers of treatment response could pave the way for earlier, more precise, and effective therapeutic interventions. Advancements in the methods used to study genetic and epigenetic mechanisms, as well as the understanding of precise brain microcircuits, foster new hope for the ability to define the broad and heterogeneous syndrome of depression as a biologically distinct disorder. Furthermore, these developments create the potential for finding more effective and faster therapies, based on in-depth knowledge of disease etiology, pathophysiology, and the dynamics of neural networks. (Akil et al., 2018)

In summary, the management of TRD requires a personalized and evidence-informed approach that accounts for patient preferences, disease severity, and treatment tolerability. Current evidence supports the use of ketamine, esketamine, atypical antipsychotics, lithium, and thyroid hormones as effective therapeutic options. However, further research is imperative to comprehensively assess their long-term safety and efficacy, thereby optimizing treatment strategies for this challenging condition.

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