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The Final Thesis

Management of Treatment Resistant Depression

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1. Abstract

Treatment-Resistant Depression (TRD) poses a substantial challenge in psychiatric care, where individuals often do not respond adequately to standard antidepressant therapies. This dissertation provides a narrative review of current literature on Treatment-Resistant Depression, with a focus on exploring treatment options, assessing their efficacy, and highlighting limitations.

Pharmacological strategies, including augmentation, combination therapy and antidepressant switching, alongside emerging treatments such as ketamine, psilocybin, buprenorphine, and dextromethorphan and non-pharmacological interventions, encompassing psychotherapeutic methods and brain stimulation techniques like electroconvulsive therapy and repetitive transcranial magnetic stimulation, can be considered when discussing the management of Treatment-Resistant Depression.

Challenges such as issues with treatment adherence and the lack of a universally accepted definition as well as the need for personalized medicine pose great challenges in the management of Treatment-Resistant Depression.

This review aims to provide valuable insights into the complexities of managing Treatment-Resistant Depression, supporting clinicians and researchers in their efforts to improve treatment outcomes for individuals facing this challenging condition.

2. Keywords

Treatment-Resistant Depression • Management • Interventions • Augmentation • Combination • Switching • Emerging treatments • Brain stimulation • Psychotherapy

3. Introduction

Depression, a complex and rather common mental health disorder, continues to cast a profound shadow over the lives of millions worldwide. According to WHO around 280 million people globally are affected by depression. Characterized by continual feelings of sadness, diminished interest or pleasure, and an array of cognitive, emotional, and physical disturbances, depression constitutes a major global health concern that significantly impacts individual well-being and societal productivity. While numerous individuals experience temporary feelings of sadness or emotional distress, clinical depression distinguishes itself as a chronic condition, which needs close attention from mental health professionals, researchers, and policymakers alike. [1]

3.1 Background and significance of Treatment-Resistant Depression

This dissertation aims to delve into the particularly challenging subset of depression known as Treatment-Resistant Depression. TRD presents an additional layer of complexity to the already intricate nature of depression, as it refers to cases where individuals do not adequately respond to antidepressant treatments. The definition and application of TRD remains a subject of ongoing debate and lack universal agreement. Different experts and researchers have varying interpretations and usages of this term, leading to a lack of consensus in the field of mental health. This creates challenges in accurately identifying and categorizing patients who do not respond adequately to conventional antidepressant treatments. As a result, the understanding of TRD may vary among clinicians, potentially affecting treatment decisions and outcomes for individuals struggling with TRD.

Using the definition that seemed to be the most widespread, TRD refers to patients, who fail to adequately respond to two consecutive antidepressant trials, which are administered at sufficient dosages for an appropriate period of time. There is no consensus regarding the definition of adequate response or adequate trial. An adequate response can be described as achieving either a state where the symptoms are relatively mild or nonexistent, or experiencing a significant improvement of at least 50% in depressive symptoms. Moreover, a trial to determine adequacy should involve using a licensed antidepressant medication at a uniform dosage, for a time span considered appropriate to produce a therapeutic effect, typically around 8 weeks.[2] While progress has been made in the field of mental health, treatment outcomes for depression have not improved significantly for all individuals. This shows an article from 2022, where it states that up to 30 % of all depressive patients are affected by TRD[3], underscoring the need to explore the challenges and intricacies associated with it.

3.2 Objective, Procedure and Methodology

The primary objective of this dissertation is to conduct a review of current literature on Treatment-Resistant Depression, with a specific emphasis on exploring various treatment modalities, evaluating their efficacy, limitations, and potential side effects. A narrative review was chosen for this and the databases which were utilized were PubMed, ResearchGate, Bmcpsychiatry and SageJournals but also articles from official government websites, ScienceDirect, springer, psychiatrist.com, International Journal of Neuropharmacology, American Journal of Psychiatry, JAMA psychiatry or Aerzteblatt were used as well as books by Klaus Lieb. Articles or books published in both English and German were included, without restrictions on publication dates. Full articles were reviewed within the timeframe spanning from 2023 to 2024.

4. Understanding Treatment-Resistant Depression

This chapter lays the groundwork for understanding Treatment-Resistant Depression by delving into its fundamental aspects. It will explore different definitions of TRD, the prevalence and epidemiology, while also examining the key factors contributing to treatment resistance.

4.1. Other definitions of Treatment-Resistant Depression

In the thesis introduction above the prevailing definition of TRD in contemporary discourse is used, which is also referred to “medication failure models”[4]. Nevertheless, there are also common alternative approaches on how to define and classify TRD, using “staging models”[4]. In 1997, Thase and Rush first proposed a classification with five distinct stages aimed to show a clearer delineation of Treatment-Resistant Depression. The severity of resistance attributed to a patient escalates with each successive stage. This progression is dependent upon the patient adhering to the recommended dosage and duration of treatment. With ascending stages, the consideration shifts towards less conventional antidepressants. However, one of the inherent flaws in this framework lies in the potential misconception that it establishes a ranking among antidepressants, implying that higher stages correspond to superior or more effective medications, a premise that lacks substantiation. Following Thase and Rush, other staging models were developed with the goal of refining the approach and although each of these models holds significance for discussion, this paper will specifically delve into one additional staging system: the European staging method, selected to provide a comprehensive

understanding of the diverse methodologies employed in the field, since it offers a different approach to staging then provided by Thase and Rush. The European Staging Method takes several factors into consideration, including the number of treatment trials, the duration of the current episode and the distinction to chronic depression. The system comprises three stages: A, designated for non-responders; B, representing Treatment-Resistant Depression (TRD); and C, characterizing Chronic Resistant Depression (CRD). Each stage is defined by specific criteria. In Stage A, nonresponse is identified by the failure to respond to a single adequate antidepressant trial. Stage B encompasses nonresponse to two or more adequate antidepressant trials, while Stage C involves resistance to multiple antidepressant trials, encompassing augmentation therapy. Furthermore, each stage is associated with a distinct trial duration. Stage A requires a trial duration of 6 to 8 weeks. For Stage B, which has sub-stages TRD 1 to TRD 5, trial durations vary: TRD 1 spans 12 to 16 weeks, TRD 2 covers 18 to 24 weeks, TRD 3 extends from 24 to 32 weeks, TRD 4 ranges from 30 to 40 weeks, and TRD 5 encompasses a duration of 35 weeks to 1 year. CRD is characterized by a trial duration exceeding 12 months.[5] This demonstrates how the European staging method identifies Treatment-Resistant Depression when the patient displays resistance to at least two adequate antidepressant trials. In comparison, the Thase and Rush model requires only one failure to an adequate trial for the definition of TRD. Furthermore, the European staging method introduces an additional stage termed "chronic resistant depression.[5]

4.2 Prevalence and epidemiology

Identifying the exact prevalence of Treatment-Resistant Depression poses a challenge, due to significant variations in estimates within the literature, primarily resulting from the absence of a standardized TRD definition. However, a noteworthy US study published in 2021, came to the conclusion, that among adults in the United States receiving medication for MDD, approximately 30.9% experienced TRD. In terms of prevalence, this implies that nearly one-third of adults with medication-treated MDD exhibit resistance to standard treatments, highlighting the significant proportion of individuals facing challenges in achieving good outcomes with conventional therapies.[6]

Additionally, a cross-sectional study was conducted to investigate the prevalence of Treatment-Resistant Depression amidst patients undergoing pharmaceutical treatment for depression in the US. The study took data from two extensive databases with a total of 573996 patients,

revealing that the prevalence of TRD hovers around 6% to 6.8% among pharmaceutically treated depression patients, with only marginal variations observed between the databases. Noteworthy insights were gained into the demographic associations of TRD, indicating that its prevalence can be influenced by factors such as biological sex, ethnicity and age group. Specifically, the study found a higher occurrence of TRD among females and individuals of Caucasian ethnicity, particularly within the age bracket of 45 to 64 years. Importantly, the absolute differences in prevalence among these demographic groups were found to be minimal.[7] These two studies effectively highlight substantial variations in estimates, likely stemming from differences in the definition of Treatment-Resistant Depression, the characteristics of the study populations, the sample sizes, and the sources of data.

4.3 Risk factors of treatment resistance

There are several risk factors thought to contribute to therapy resistance, which will be briefly discussed in the following chapter. However, to do so, it is essential to differentiate between therapy resistance and pseudo resistance. Pseudo-resistance occurs when a patient does not adequately respond to treatment due to misdiagnosis, noncompliance, or incorrect treatment. In other words, patients who are pseudo-resistant may become non-resistant if the root cause of pseudo-resistance is addressed. A German article from 2014 identifies several factors that can contribute to pseudo-resistance, including inadequate treatment, patient noncompliance for various reasons, misdiagnoses, or pharmacologically induced depression.[8] Therefore, to effectively help patients with Treatment-Resistant Depression, it is crucial to first rule out pseudo-resistance as a potential cause of the problem.

A noteworthy cohort study, published in the BMC Psychiatry came to the conclusion, that especially females are at a higher risk to develop TRD then their male counterpart. They exhibited a 7,22% elevated likelihood of suffering from TRD compared to males, suggesting that female gender holds a significant impact on TRD susceptibility. Significant association between financial circumstances and TRD was also found by this study since they found that within the TRD-afflicted group, a notable 21.82% lacked any source of income, whereas this percentage was comparatively lower at 16.3% in the non -TRD group. The cohort study also suggests that comorbidities play an important role when looking at the risk factors of TRD, notably, conditions such as anxiety disorder, panic disorder, non-organic psychosis, and personality disorders emerged as substantial contributors to TRD risk.[9]

Interestingly, a base cohort study published in 2022, originating from Finland, yielded divergent findings concerning the relationship between gender and heightened susceptibility

to Treatment-Resistant Depression. Contrary to prevailing trends, this study revealed that males were positioned at a higher risk of developing TRD compared to females. The authors of this study acknowledged that their results contradicted the outcomes of previous investigations. They further pointed out that this discrepancy might stem from the fact that males are more inclined to underutilize mental health support services compared to their female counterparts.[10] Non-psychiatric ailments like diabetes, systemic lupus erythematosus (SLE), GI disorders, heart diseases and thyroid dysfunction also displayed an association with increased TRD susceptibility, with gastrointestinal disorders presenting the highest risk for developing TRD.[11] The exploration of genetic factors is pivotal when assessing TRD risk. Notably, genes such as RIK4, BDNF, SLC6A4, and KCNK2 have been investigated, exhibiting suggestive associations with TRD, although comprehensive cohort studies could not validate these findings. Pathways like neuronal plasticity have been implicated in TRD but further in-depth investigations are necessary. The current landscape lacks established genetic biomarkers for identifying individuals at elevated TRD risk, which emphasizes the need for continued research in that field. [12]

These diverse findings show the complex interplay between gender, genetics, socioeconomic factors and comorbidities and underscores the complex nature of TRD susceptibility.

5. Treatment options of TRD

The impact of TRD on individuals is substantial. People with TRD face a higher risk of suicide compared to those without TRD. Additionally, they experience more severe impacts on their Quality of Life, with greater depression severity and functional impairment.[13]

This underscores the heavy burden that TRD places on individuals and emphasizes the urgent need for effective treatment strategies. In the upcoming chapters, a wide range of treatment options will be explored.

5.1 Pharmacological treatment options

With the goal of alleviating the profound burden of TRD, the exploration of pharmacological interventions stand as a cornerstone of therapeutic advancements. This chapter discusses the complexity of pharmacological interventions, including both established approaches and emerging therapies, showing the evolving landscape of TRD treatment. The aim is to navigate the complex interplay between traditional medication and novel breakthroughs.

Revisiting the most commonly clinical definition, the diagnosis of TRD necessitates the

occurrence of two unsuccessful trials with adequate doses and a sufficient time period. Upon confirming this condition and eliminating the possibility of pseudo-resistance, a variety of pharmacological strategies come into play for its management. These include incorporating adjunctive treatments or using a combination of antidepressants, including exploring the utilization of innovative therapeutic agents.[14]

5.1.1 Augmentation strategies

Augmentation strategies are used to amplify the efficacy of conventional antidepressants. In the context of pharmacotherapy, augmentation entails the addition of a supplementary medication to the established regimen, aiming to heighten the therapeutic impact.[15]

In 2020, a study published in the International Journal of Neuropsychopharmacology, conducted a comprehensive examination of prevailing treatment guidelines, encompassing a comprehensive analysis across ten distinct guidelines. Drawing upon the findings, the study identified 3 augmentation therapies, that garnered recurrent recommendations across multiple guidelines: Atypical Antipsychotics, Lithium, and Thyroid hormones. Both Atypical Antipsychotics and Lithium stood out, having been approved as augmentations therapies by all ten scrutinized guidelines. Atypical Antipsychotics emerged as a 1st line recommendation in seven guidelines, while two guidelines proposed it as a 2nd line intervention, and one guideline endorsed it without specifying its priority. In the case of Lithium, five guidelines positioned it as a first-line augmentation, two as a second-line option, and three endorsed it without hierarchical distinction. Thyroid hormone, as an augmentation approach, secured a second-line status in half of the guidelines, while two guidelines omitted its recommendation entirely. Two guidelines advocated for Thyroid hormone as a first-line strategy, while one guideline included it devoid of specified hierarchy.[16]

In light of these revelations, the subsequent scrutiny will be directed towards a thorough examination of the three most recommended augmentation therapies.

Atypical Antipsychotics, also known as 2nd Generation Antipsychotics, employ a different mechanism of action in comparison to their counterparts, the Typical or 1st Generation Antipsychotics. Unlike the Typical Antipsychotics, Atypical Antipsychotics typically exhibit less affinity for binding to the D2 receptors. Instead, they engage with a diverse array of receptors, with exceptions being Amisulpride and Aripiprazole, who have a stronger D_2 affinity. Among the receptors that Atypical Antipsychotics interact with are m-ACh, alpha 1, D_2, 5-HT_2, H_1, D_1, alpha 2, D_4, 5-HT_{2a}, 5-HT_{2c} and 5-HT_1.[17] AAs are reputed to enhance the transmission of neurotransmitters such as serotonin, norepinephrine, and dopamine independently,

while also mitigating the inhibitory effects on firing activity in monoamine-secreting neurons caused by certain antidepressant drugs.[18]

It's worth noting that typical Antipsychotics do not exclusively bind to D2 receptors, but they often display a higher binding affinity to D2 compared to Atypical Antipsychotics. This heightened affinity can lead to the emergence of extrapyramidal symptoms, a side effect less pronounced in Atypical Antipsychotics. However, Atypical Antipsychotics do present with other adverse effects, for example an increased tendency for weight gain.[19]

In 2015, a noteworthy network meta-analysis delved into the augmentation strategy employing atypical antipsychotics for Treatment-Resistant Depression. The study aimed to scrutinize the comparative efficacy and tolerability of adjunctive AAs in TRD, encompassing various AA types and dosages with a total of 4422 patients. The AAs employed for augmentation included Aripiprazole, Olanzapine, Quetiapine, and Risperidone. Patients undergoing this augmentation were taking SSRI/SNRI antidepressant. The study compared both low dosages and standard doses.

Regarding primary efficacy results, all standard dose agents exhibited significantly greater effectiveness in comparison to placebo, whereas this significance was not observed for the low dose group. When considering tolerability, all standard doses, except for risperidone, were associated with a notably higher incidence of side effect-related discontinuation when contrasted with the placebo group.

Furthermore, the study's findings highlighted that, considering quality of life improvement, both standard dose risperidone and aripiprazole showcased more positive effects compared to the placebo. Additionally, standard dose risperidone outperformed quetiapine in terms of efficacy.[20]

These findings found further substantiation in additional research, exemplified by a network meta-analysis released in 2022. This study not only evaluated the effectiveness of augmentation agents in patients with Treatment-Resistant Depression, similar to the 2015 study by Zhou, but also extended its scope to include agents such as T4 or Lithium. The analysis arrived at the same conclusion as Zhou's study, reinforcing the reliability of the results.

Within this 2022 study, a broader spectrum of atypical antipsychotics was investigated. Notably, brexpiprazole and cariprazine were identified as having superior efficacy compared to the placebo. However, it's noteworthy that cariprazine exhibited lower acceptability in comparison to placebo within the study.[21]

Another augmentation therapy option is lithium augmentation therapy. Lithium, a mood-stabilizing medication, stands as the gold standard in treating bipolar disorder. However, its

utility extends beyond bipolar disorder, encompassing augmentation treatment of depression as well.

Research indicates that lithium can prove effective in cases where patients have shown inadequate responses to solely tricyclic antidepressants or selective serotonin reuptake inhibitors. The mechanism underlying the augmentation is thought to involve increasing serotonin transmission in a synergistic manner alongside antidepressants and exerting inhibition on glycogen synthase kinase 3ß, yielding a neuroprotective effect.[22]

In a recent meta-analysis, the comparative efficacy and risk of adverse effects were evaluated for lithium, AA, and Esketamine in contrast to placebo. The findings of this analysis indicate that lithium not only exhibited superior effectiveness but was also better tolerated when compared to both AA and Esketamine. However, it is important to note that a significant proportion of the trials exploring the augmentation of lithium primarily focused on older antidepressants, particularly TCAs.[23]

The efficacy of Lithium was further bolstered by the meta-analysis conducted by Nuñez, which underscored the superiority of lithium when contrasted with placebo and while a distinct superiority in effectiveness was not observed across all AAs, it was evident in certain cases.[24]

A recent study delved into the genetic correlations between antidepressant response, lithium response, and Treatment-Resistant Depression. The findings revealed an intriguing pattern: patients with TRD exhibited a decreased genetic predisposition for antidepressant response and a notably elevated genetic predisposition for lithium response, in comparison to non-TRD cases. Although this exploration provides valuable insights, a comprehensive investigation is warranted to validate and expand upon these outcomes. Such research holds promise in potentially aiding individuals with TRD and shedding further light on the genetic foundations behind the effects of lithium.[25]

Liothyronine (T3) also presents as a viable augmentation therapy worth contemplating for TRD patients. While the precise mechanism of T3's effectiveness in augmentation therapy remains somewhat elusive, it is hypothesized to entail both nuclear-level interactions that stimulate gene transcription, as well as cell membrane-related processes that enhance neurotransmission. Notably, there is compelling evidence suggesting that T3 augments the effects of the neurotransmitter 5-HT, which underscores its potential significance.[26]

The aforementioned 2022 meta-analysis by Nuñez extended its scope to include T3 in its investigation, evaluating its efficacy and discontinuation rates alongside other agents such as

AAs and Lithium. The analysis yielded a noteworthy finding, indicating that T3 not only demonstrated enhanced efficacy over placebo but also achieved a level of comparability with lithium.[27]

These findings align with the results of the 2015 NMA conducted by Zhou and colleagues with 6654 participants. Their study, revealed that, in terms of efficacy, thyroid hormone is statistically more significant compared to placebo. However, their analysis also uncovered that the majority of sensitivity analyses pointed to a stronger efficacy estimates for aripiprazole and quetiapine, in comparison to thyroid hormone or lithium. The study also underscored a notable discrepancy in tolerability, with quetiapine displaying significantly reduced tolerance in contrast to thyroid hormone. This apparent advantage in favor of T3, however, was counterbalanced by Zhou and colleagues' assertion that due to the superior efficacy values observed for quetiapine and aripiprazole, these two agents could be regarded as the most compelling evidence-supported choices for augmentation therapy in adults dealing with TRD.[28]

In contrast, a separate meta-analysis published in 2020, encompassing a total of 663 patients, arrived at the finding that thyroid hormone therapy, when employed as an adjunctive treatment in individuals with TRD, did not demonstrate superiority over either placebo or lithium.[29] Nuñez and colleagues elucidated that the disparity in these outcomes could stem from variations in study populations, research design, or the diverse definitions of Treatment-Resistant Depression.[30]

This collective body of research contributes to a growing consensus regarding the efficacy and comparative performance of augmentation strategies, involving atypical antipsychotics, lithium or T3 in addressing Treatment-Resistant Depression.

5.1.2 Combination therapy

Augmentation isn't the exclusive pharmacological intervention available for treating TRD. Combination therapy offers another viable approach, living up to its name by combining two drugs of the same substance group to achieve a synergistic effect. In contrast, augmentation therapy involves introducing a different substance call to an ongoing treatment regimen, with the intent of amplifying its effectiveness.[31]

A 2022 meta-analysis delving into the dynamics of combined versus monotherapy treatments for acute depression provides valuable insights into the potential of combination therapy for individuals dealing with TRD. This comprehensive analysis, which included 39 studies and a total of 6751 patients, came to the conclusion, that in terms of efficacy, 82% are in favor of combination treatment, when comparing it to monotherapy.

Specifically, when examining non-responders, the pairing of a monoamine reuptake inhibitor with an antagonist of presynaptic alpha 2 auto-receptors demonstrated superior outcomes relative to monotherapy, yielding statistically significant yet modest effect sizes. The authors of this meta-analysis concluded that patients resistant to conventional treatments pose a challenge, and the observed small effect sizes stem from comparisons with active treatments, which tends to lead to lower estimates of efficacy.[32]

When deliberating upon the selection of an antidepressant for combination therapy, the literature suggests mirtazapine, bupropion, and agomelatine as they stand out for their favorable tolerability profile and minimal drug-drug interactions.[33]

The safety of combining mirtazapine with venlafaxine is further supported by the STAR*D study, a landmark investigation published in 2006 and renowned as the largest antidepressant study ever conducted. The study's primary objective was to aid clinicians in determining the optimal subsequent treatment for patients who exhibited an inadequate response to their initial antidepressant regimen. In this study, patients were assigned to different levels of treatment. At Level 1, citalopram was administered. Level 2 introduced seven treatment options, including four switch therapies where citalopram was replaced by sustained-release bupropion, cognitive therapy, sertraline, or extended-release venlafaxine. Additionally, three augmentation therapies were explored: citalopram plus bupropion, buspirone, or cognitive therapy. Moving to Level 3, two switch therapy options were offered: mirtazapine or nortriptyline, alongside two augmentation options involving lithium or T3. Finally, Level 4 encompassed a solitary randomization, where patients were assigned to either tranylcypromine or extended-release venlafaxine plus mirtazapine.[34]

Among the extensive cohort of over 4,000 participants, a subset of 109 individuals progressed to Level 4. Out of this group, 58 were assigned to receive tranylcypromine, while 51 were allocated to the combination treatment involving extended-release venlafaxine and mirtazapine. In essence, the STAR*D study serves as a testament to the superior tolerability of the combination therapy involving mirtazapine and venlafaxine, since this combination exhibited fewer adverse effects when compared to tranylcypromine. A higher number of participants on tranylcypromine withdrew from the study due to side effects. It is worth highlighting that both strategies had rather low rates of remission and response, with no statistically significant disparities detected between the two groups in terms of remission and response outcomes. However, due to its notably better tolerability, the combination of mirtazapine and venlafaxine should be considered in patients with TRD and despite the relatively modest remission rate, this combination has demonstrated its ability to provide valuable assistance to a subset of patients.[35]

Another combination is explored in a study conducted in 2008, which closely examined the combination of olanzapine and fluoxetine (OFC) for treating TRD while assessing both efficacy and clinical utility with the result that OFC does prove beneficial in decreasing Montgomery-Asberg Depression Rating Scale scores following an insufficient response to antidepressant monotherapy. However, the study highlighted the presence of diverse side effects, emphasizing the necessity to comprehensively assess the associated risks and benefits when considering the viability of this option.[36]

These findings were further corroborated by a pooled analysis conducted in 2010, which concurred with the notion that OFC surpasses both fluoxetine and olanzapine when employed as a monotherapy, particularly in generating early improvements for patients with TRD.[37]

5.1.3 Switching antidepressants

Using a different antidepressant is an alternate strategy that clinicians can employ to prompt a patient's response when the initial antidepressant proves ineffective. Reflecting on the earlier-mentioned STAR*D study, Level 1 of the study entailed initiating treatment with citalopram, an SSRI. Subsequently, at Level 2, the study introduced three distinct pharmacological switch therapies. In these, citalopram was substituted with sustained-release bupropion, sertraline, or extended-release venlafaxine. Advancing to Level 3, patients were presented with two switch therapy alternatives: mirtazapine or nortriptyline and Level 4 only offered two options in general: switching to tranylcypromine or mirtazapine combined with venlafalxine.[38]

In the initial phase, the remission rate measured by HAM-D, stood at 33%. Transitioning to the second phase, it is noteworthy that 57% of participants who progressed to this step willingly underwent randomization for the three switch options. Although the aforementioned switch options are known to influence interconnected neurotransmitter systems, this influence failed to manifest clinically significant distinctions in practice. In fact, the remission rates determined by $HRSD_{17}$ demonstrated remarkable similarity, hovering at approximately 25-27%, a mere discrepancy of 1 to 2 percent. Similarly, the time required to achieve remission displayed no noteworthy variations among the three options.[39]

Regrettably, the pursuit of identifying the superior therapy between switching and augmentation strategies is hindered by inherent challenges. Variations in the severity of depression upon entry into the subsequent level, coupled with limited sample sizes, have impeded a direct head-to-head comparison of these approaches. In fact, it is worth noting that individuals who opted for a switch to a new medication demonstrated a higher degree of illness severity compared to those who underwent augmentation or cognitive therapy.[40]

During the third phase, where patients had the option to switch to either mirtazapine or nortriptyline, the assessment of remission response, as gauged by $HRSD_{17}$, indicated a remission rate of 12% for mirtazapine and 20% for nortriptyline. Like in phase 2, the remission and response rates for these two alternatives displayed no statistically significant differences, and in terms of side effects, no meaningful distinction emerged either.
It's notable that less than 20% of the individuals experiencing depression achieved remission upon transitioning to an alternative antidepressant after undergoing two unsuccessful medication treatments within the STAR*D study. Regrettably, a comparison between augmentation and switching strategies is again constrained due to insufficient sample size.
In the fourth phase, where patients had the option to switch to either tranylcypromine or the combination of mirtazapine and venlafaxine, the outcomes in terms of HRSD17 remission rates were notably modest: 7% for tranylcypromine and 14% for the combination approach. As with the preceding phases, there was a lack of discernible differentiation between the two groups regarding remission and response rates, largely again due to the limitations imposed by the small sample size.[41]
These findings underscore the potential efficacy of switching antidepressants as a viable approach in addressing TRD. While the rates of remission during steps 3 and 4 might not be high, it remains noteworthy that a subset of patients still achieve this positive outcome.
The viability and practical relevance of switching to an alternative antidepressant medication is further emphasized by the inclusion of this strategy in the German national guideline's algorithm for managing patients who do not respond to monotherapy[42], or by the inclusion in the American Psychiatric Association's Practice Guideline.[43]
As such, the option of switching antidepressants should indeed be taken into careful consideration for the management of TRD.

5.1.4 Emerging pharmacological treatments

The previously mentioned pharmacological treatment approaches have been more or less extensively researched for quite some time. However, there are also some other and more novel treatments on the horizon for managing TRD. These treatments, either currently under evaluation or already approved due to their demonstrated efficacy, will be the central focus of the upcoming chapters, illuminating the latest research conducted in this area.

5.1.4.1 Ketamine

Ketamine made its initial debut in the 1960s primarily as an anesthetic, but it was subsequently discovered to possess antidepressant properties.[44]

The swift antidepressant effect of ketamine is understood to be mediated through the blockade of NMDA receptors found on inhibitory interneurons, leading to the disinhibition of pyramidal cells, resulting in a surge of glutamatergic transmission. Thereafter, the activation of AMPA receptors is deemed necessary for the antidepressant effect to manifest. However, it is noteworthy that other NMDA antagonists have failed to replicate the sound antidepressant action observed with ketamine. This has prompted a reconsideration of the assumption that NMDA inhibition is the central mechanism behind ketamine's antidepressant effect in rodents. It's worth noting that the complete comprehension of the interplay between ketamine and its antidepressant effects remains an active area of experimental investigation.[45]

One of the pioneering placebo-controlled, double-blind trials involving Ketamine took place in the year 2000. This study aimed to evaluate the effects of a single dose of the NMDA receptor antagonist in patients with depression. Seven participants successfully completed the trial, revealing a noteworthy outcome: intravenous ketamine treatment resulted in a marked decline in depressive symptoms, with noticeable improvements emerging progressively within just three days. It's important to highlight that the sensation of being "high" returned to baseline levels within three hours following the infusion. However, it's essential to acknowledge a potential limitation of the study. The researchers noted that the patients were able to distinguish between the placebo and ketamine treatments. This ability to discern between the two may have introduced bias, as individuals who believed they received the placebo might have reported a reduced placebo effect. This recognition of treatment status could have influenced the study's blinding integrity.[46]

A recent 2020 meta-analysis not only reaffirms findings from the year 2000 but also places particular emphasis on patients with TRD. In the case of TRD patients, the analysis concluded that the significant benefits of a single dose of ketamine compared to control groups remained mostly steady. Specifically, around 50% of TRD patients reported a positive response at 24 hours after receiving ketamine, compared to a mere 6% within the control groups. This positive response was observed whether ketamine was used as a standalone treatment or as an adjunct to ongoing antidepressant therapy. However, it's worth noting that within the context of TRD, the responsiveness to ketamine treatment appears to be influenced by various factors, including the presence of suicidal ideation, the degree of resistance to prior treatments, and the specific dosing regimen. It is suggested that TRD patients, especially those with high levels of treatment resistance, may benefit from higher doses of ketamine to achieve the desired therapeutic effects and that more research is necessary.[47]

A recent 2022 systematic review and meta-analysis further underscore the therapeutic benefits of ketamine for individuals with Treatment-Resistant Depression.

The findings of the study showed that TRD patients treated with Ketamine do experience remission less frequently compared to non-TRD patients, however, when it comes to symptom improvement (response), there was no significant difference between the two groups and therefore both TRD and non-TRD patients saw improvements in their symptoms and benefited from Ketamine. Furthermore, the study revealed that repeated use of ketamine did not result in a decline in its effectiveness over time and this sustained effectiveness was statistically significant, which is promising for long-term treatment strategies.[48]

Comparing Ketamine to other available treatment options, an interesting study from 2023 revealed that Ketamine was not inferior to Electroconvulsive therapy in treating TRD patients without psychosis[49] and a 2020 meta-analysis concluded that NMDA therapies had the highest likelihood of proving efficacious as an augmentation TRD treatment compared to other pharmacological options[50].

In the context of treatment guidelines for TRD, some recommend the use of Ketamine for TRD, while others do not. A systematic literature search conducted in 2020, previously mentioned in this thesis, identified current treatment guidelines published in English. The findings revealed that out of these guidelines two guidelines recommend Ketamine without specifying the level, one guideline suggests it as a second-line therapy, three guidelines do not recommend Ketamine and four guidelines did not discuss Ketamine as a treatment option.[51]

it's important to note that the FDA has not approved the use of ketamine for the treatment of psychiatric conditions. Instead, Esketamine, a chemically related variation of ketamine, stands as the sole FDA-approved variant of ketamine designated for the treatment of depression and suicidality.[52]

In a 2023 observational study that examined the effectiveness and treatment duration required for remission and response with repeated administrations of IV Ketamine and IN Esketamine came to the conclusion, that both intravenous Ketamine and intranasal Esketamine achieved comparable response and remission rates in patients with TRD. Notably, achieving remission demanded significantly fewer treatments with intravenous ketamine in contrast to intranasal Esketamine but further studies are needed.[53]

A 2020 article raises a cautionary flag regarding the use of ketamine as a treatment option. It highlights the importance of being careful because the studies conducted thus far are relatively small and have suggested potential risks, such as abuse, addiction, and numerous

side effects associated with ketamine. The authors underscore the need for additional research.[54]

In summary, the use of ketamine remains a subject of ongoing debate, emphasizing the necessity for further testing and investigation.

5.1.4.2 Psilocybin

When considering new treatment options for Treatment-Resistant Depression (TRD), there is increasing interest in psychedelic drugs, particularly psilocybin, within the literature. Psilocybin is an alkaloid found in nature in mushrooms of the Psilocybe genus. It acts as a non-selective agonist at numerous serotonin receptors, with a particular affinity for serotonin 5-HT2A receptors. The precise pharmacodynamic mechanisms responsible for its antidepressant effects are not fully understood. However, they are believed to involve the modulation of the serotonin system and potential indirect effects on other systems such as dopaminergic and glutamatergic pathways and is thought to influence e.g. neural circuitry and the amygdala.[55]

In 2016, one of the early pioneering studies exploring the use of Psilocybin for Treatment-Resistant Depression was conducted. This open-label feasibility trial involved 12 patients. Notably, the study reported that patients did not experience any serious adverse effects, and their depressive symptoms remained low even three months after receiving a high-dose treatment.[56]

Another noteworthy study from 2021, involving 59 patients with mild to moderate depression, was conducted to compare Psilocybin to escitalopram. This randomized trial spanned six weeks and found no statistically significant disparity in depression scores between the two treatment agents.[57]

More specific for TRD was a double-blind study which was conducted in 2022 and had 233 treatment resistant patients. The participants were randomly assigned to receive a single dose of synthetic psilocybin at three different dosage levels: 25mg, 10mg, or 1mg.

The results showed that those who received the 25mg dose experienced a significantly greater reduction in MADRS total scores (a measure of the severity of depressive episodes) at the 3rd week compared to those who received the 1mg dose. There was no notable difference between the 1mg and 10mg dosage groups. It's important to note that the higher 25mg dose was associated with more adverse effects in patients.[58]

Overall, it can be suggested that psilocybin shows promise as a potential treatment for TRD. However, further trials and studies are needed to confirm its efficacy and safety.

A promising study, which commenced recruitment in May 2023 and is expected to span approximately 36 months, aims to explore if the psychedelic effects of psilocybin is essential for its effectiveness in treating TRD and it aims to assess the safety and effectiveness of administering psilocybin and risperidone in combination. Additionally, the study intends to provide valuable data regarding the antidepressant potential of this combined treatment approach.[59]
This study has the potential to yield novel insights, but it remains to be seen which new information it may provide.

5.1.4.3 Buprenorphine

Another option for the treatment of Treatment-Resistant Depression might be found in Buprenorphine. This medication, classified as an opioid, stands out due to its distinctive mechanism of action. It functions as a partial agonist of mu opioid receptors while simultaneously acting as an antagonist of kappa and delta opioid receptors.[60]
One of the newer trials found, that researched the use of buprenorphine in the context of Treatment-Resistant Depression was published in 2014, with 13 subjects that completed the trial. The findings of this study indicated that there was an observable improvement in depression symptoms within the first week of initiating buprenorphine treatment. However, the observation was made that when Buprenorphine was discontinued, the subjects experienced a resurgence of depressive symptoms. This suggests that a prolonged or long-term treatment with Buprenorphine may be necessary to sustain its antidepressant effects over an extended period.[61]
These findings align with an earlier study conducted in 1995 involving seven participants with Treatment-Resistant Depression. In that study, significant improvements were observed in both subjective and objective measures of depression when treating with Buprenorphine.[62]

Also in favor of Buprenorphine, is a study published in 2015. It revealed that the combination of Buprenorphine and Samidorphan, an opioid antagonist, especially at a 1:1 ratio, led to significant improvements in depression symptoms in TRD patients. The combination also seemed to reduce the potential for addiction to Buprenorphine, and there were no signs of opioid withdrawal when the treatment was stopped. Interestingly, the most robust antidepressant effects were seen with the 1:1 ratio, which was unexpected. This suggests that a balanced combination of opioid agonist and antagonist activities may be more effective in treating depression than previously thought.

The study also mentions the potential role of the κ-opioid system in depression and suggests that further research is needed to fully understand how this combination treatment works.[63]

While the previously mentioned results sound promising, it's important to note that a meta-analysis published in 2020 painted a somewhat different picture. This analysis included six studies, and it found that the severity of depression symptoms in Treatment-Resistant Depression patients did not significantly decrease when Buprenorphine was used as an adjunctive intervention compared to a placebo, whether used alone or in combination with Samidorphan. However, the authors of the meta-analysis did acknowledge that higher doses of Buprenorphine might have the desired effect. As such, they did not entirely dismiss it as a potential treatment option.[64]
In summary, further research is required to gain a more comprehensive understanding of the potential benefits and limitations of Buprenorphine as a treatment option.

5.1.4.4 Dextromethorphan

Dextromethorphan is a well-known cough suppressant. However, it has shown potential as an antidepressant in limited human studies and animal trials. Its mechanisms of action include acting as a glutamate N-methyl-D-aspartate receptor antagonist, a sigma-1 receptor agonist, and an inhibitor of serotonin reuptake.[65]
In a phase IIa open-label clinical trial published in 2017, researchers examined the effectiveness and tolerability of a combination therapy involving Dextromethorphan and Quinidine in patients with Treatment-Resistant Depression. The results indicated that the combination, specifically at doses of up to 45/10mg administered every 12 hours, was effective in reducing depressive symptoms, and patients generally tolerated it well. The study emphasized the importance of conducting future larger placebo-controlled randomized trials in TRD patients to further investigate its potential.[66]
Another open-label study from 2023, that also investigating the combination of Dextromethorphan and Quinidine in patients with Treatment-Resistant Depression, yielded promising outcomes as well. This study involved 17 participants, and notably, nearly half of them achieved a full response, defined as a reduction of at least 50% in their baseline MADRS score, while 35% achieved a partial response, signifying a 25% to 50% decrease in their baseline MADRS score. Importantly, none of the patients experienced severe side effects. The study's authors also emphasized the necessity for larger, placebo-controlled trials to further explore this potential treatment approach.[67]

Another combination therapy, Dextromethorphan with Bupropion or also known as AXS-05, was explored in a 2019 phase 3 double-blind trial. This trial involved 327 patients diagnosed with Major Depressive Disorder according to DSM-5 criteria. Participants were randomly assigned and evenly divided to receive either AXS-05 or a placebo. The results demonstrated that AXS-05 led to a significant improvement in depressive symptoms compared to the placebo and was well-tolerated by the patients.[68]
More specific to TRD, a case report published in 2023 reported promising result with the use of AXS-05, where significant symptom improvement was observed. This individual had TRD along with psychiatric comorbidities. The combination therapy effectively addressed symptoms of depression and suicidal behavior. However, the report emphasized the need for additional studies to arrive at safer and more conclusive recommendations for these patients.[69]

To sum up it can be said Dextromethorphan and its combinations hold promise, but ongoing exploration is necessary for a comprehensive understanding of their role in addressing TRD.

5.2 Non-pharmacological treatment options

The upcoming chapters will delve into non-pharmacological treatment options for Treatment-Resistant Depression. These approaches include psychotherapy techniques, brain stimulation methods like Electroconvulsive Therapy (ECT), Repetitive Transcranial Magnetic Stimulation (rTMS), and Deep Brain Stimulation (DBS), along with emerging interventions such as Transcranial Direct Current Stimulation (tDCS), Vagus Nerve Stimulation (VNS), and Light Therapy. This exploration will focus on how these interventions can be particularly effective in addressing the complexities of TRD, offering potential breakthroughs in treatment beyond conventional medication-based approaches.

5.2.1 Psychotherapy approaches

Psychotherapy approaches are integral components in the comprehensive management of depression. These therapeutic interventions, whether used alongside pharmacotherapy or as standalone treatments, hold a significant role in effectively managing depression[70] and are also deployed in TRD.
In a recent 2018 article, the effectiveness of psychotherapies for adults with TRD was evaluated. The study encompassed six trials involving 698 participants, primarily middle-aged women.

Different types of psychotherapy, including cognitive-behavioral therapy (CBT), intensive short-term dynamic psychotherapy (ISTDP), interpersonal therapy (IPT), and group dialectical behavioral therapy (DBT), were incorporated alongside standard care and compared to standard care alone, with standard care meaning treatment with antidepressants. The analysis revealed that supplementing standard care with psychotherapy led to a noticeable improvement in self-reported depressive symptoms for up to six months. This improvement was consistently observed across different depression measurement scales. The quality of evidence supporting these improvements was considered moderate. Psychotherapy was also shown to enhance remission and response rates in TRD patients. Additionally, cognitive-behavioral therapy was associated with lower depression scores over both medium and long-term durations.[71]

A randomized controlled trial further reinforces the efficacy of psychotherapy, specifically Cognitive Behavioral Therapy, used alongside pharmacotherapy for patients with Treatment-Resistant Depression. This study involved 469 participants, with 234 in the intervention group (receiving usual care plus Cognitive Behavioral Therapy) and 235 in the usual care group. At the 6-month mark, 46.1% of individuals in the intervention group attained a response to treatment, compared to only 21.6% in the usual care group. Repeated measures analyses, considering data from both the 6-month and 12-month time points, consistently demonstrated positive outcomes for the intervention group, with an odds ratio of 2.89 for response and 2.74 for remission.[72]

These results suggest that the addition of CBT is effective in improving treatment outcomes for individuals with Treatment-Resistant Depression.

In the previously mentioned STAR*D Study, cognitive therapy was explored as a treatment option for patients with Treatment-Resistant Depression. Among the 182 patients who found cognitive therapy acceptable, they were randomly assigned to either the cognitive therapy switch option or the augmentation of citalopram with cognitive therapy. The study's findings revealed that patients who opted for cognitive therapy achieved remission rates on par with those who switched to different antidepressants or underwent medication augmentation. These results underscore the effectiveness of cognitive therapy as a viable treatment approach for some individuals dealing with TRD. Furthermore, it's noteworthy that transitioning to cognitive therapy was associated with better tolerability and fewer side effects compared to switching to alternative antidepressants. This highlights the potential advantages of cognitive therapy, particularly in terms of its tolerability profile and reduced risk of side effects, which could make it a preferred choice for certain patients.

However, it's essential to consider that while remission rates were similar between cognitive therapy and medication-based approaches, medication augmentation demonstrated a quicker onset of response. This suggests that, for individuals seeking a more rapid improvement in their depressive symptoms, initiating treatment with medication augmentation may be a more suitable initial strategy.[73]

The results suggest that cognitive therapy can be a viable option for the treatment of TRD, especially as an augmentation therapy.

In a 2018 meta-analysis and meta-regression analysis, further insights into the role of psychotherapy in treating TRD were uncovered. This comprehensive analysis involved 21 trials encompassing seven distinct psychotherapeutic approaches, resulting in 25 comparisons. Interestingly, the findings indicated that there wasn't substantial evidence to suggest that psychotherapy offered a significant advantage over standard Treatment as Usual (TAU) when directly compared. However, when examining 22 comparisons that involved augmenting psychotherapy alongside TAU versus TAU alone, a noteworthy pattern emerged. Here, the data revealed a moderate positive effect size (0.42) in favor of combining psychotherapy with TAU. This suggests that the inclusion of psychotherapy alongside standard treatment can indeed enhance therapeutic outcomes for individuals dealing with TRD. Furthermore, the meta-regression analysis provided valuable insights. It showed that the effectiveness of psychotherapy was positively correlated with the initial severity of depression symptoms. In simpler terms, psychotherapy appeared to be more beneficial for individuals with more severe depressive symptoms. Additionally, the format of therapy played a role, with group therapy demonstrating a more positive treatment effect when compared to individual therapy.[74]

Drawing from various sources, including the findings of Bronswijk, a recent article states that it becomes evident that our current definitions of Treatment-Resistant Depression are overly restrictive, failing to acknowledge the potential merits of psychotherapy. This observation highlights the need for a more comprehensive and inclusive approach to TRD.

Moreover, the article states the significance of psychotherapy in the TRD landscape should not be underestimated. Many individuals grappling with depression express a preference for psychotherapeutic interventions, highlighting the importance of considering patient choice in treatment decisions. This preference can significantly influence treatment outcomes, making it an essential factor to incorporate into the broader discourse on TRD management.[75]

In summary, evidence suggests, that psychotherapy should not be dismissed as a valuable treatment option for individuals with TRD and might warrant inclusion in the broader definitions of this condition.

5.2.2 Brain stimulation techniques

In the domain of Treatment-Resistant Depression, where conventional therapies often fall short, new options have emerged through Brain Stimulation Techniques. This section delves into the approaches that have redefined how we combat the resilience of depression in individuals who have not found relief through standard interventions.

5.2.2.1 Electroconvulsive therapy (ECT)

ECT is a therapeutic approach primarily employed for individuals dealing with severe major depression or bipolar disorder that has proven resistant to other interventions. It is also considered for individuals in urgent need of a fast treatment response and for catatonia. The efficacy of ECT in addressing severe mental disorders is widely acknowledged by esteemed institutions.[76]

The precise mechanism by which ECT operates remains a subject of ongoing investigation, though substantial progress has been achieved in recent years. Various theories have surfaced regarding its mode of action, broadly categorized into neurophysiological, neurobiochemical, and neuroplastic mechanisms. These hypotheses encompass an array of factors, including neurotransmitters, neurotrophic agents, the immune system, the hypothalamic–pituitary–adrenal axis, neuroplasticity, epigenetic modifications, brain neurophysiology, circuitry, and structure. In the last 20 years, there has been a notable transition towards a theory positing that ECT exerts its effects through the induction of neuroplastic changes.[77]

In 2018, the FDA made significant changes regarding the use of Electroconvulsive Therapy. Before these changes, all ECT devices were categorized as Class III, which represents the highest level of risk among medical devices. Specific conditions, such as severe depression and catatonia (more precisely, individuals with severe depressive episodes associated with major depressive disorder or bipolar disorder who are 13 years and older), were approved for ECT treatment. However, the FDA decided to alter this classification. They reclassified the use of ECT for severe depression and catatonia to Class II, a category that denotes devices of moderate risk. Importantly, this reclassification allows for a more streamlined approval process for ECT in these specific cases. Moreover, it's crucial to note that the FDA's decision doesn't restrict doctors from using ECT "off-label." This means that physicians can still consider ECT as a treatment option for patients who don't precisely meet the FDA's outlined criteria but are believed to benefit from it based on clinical judgment.[78,79]

The impact of this decision is profound for patients struggling with severe depression. It ensures their continued access to ECT, emphasizing its importance as a treatment option for those who have not responded to other therapies.[80]

Also, by reclassifying ECT as Class II for depression, the FDA recognizes that the potential benefits of ECT in treating severe depression outweigh the associated risks, provided that specific controls and requirements are adhered to. Ultimately, this decision upholds ECT as a valuable option for patients while maintaining necessary safety measures.

Now that the procedure's relative safety is established, as indicated by approvals from regulatory bodies like the FDA, the attention will be turned to evaluating its effectiveness in TRD patients by reviewing relevant literature.

When examining said literature, some researchers have suggested that patients with TRD may not respond as favorably to ECT compared to non-TRD patients. A study conducted in 1996, which examined short-term clinical responses to ECT, reached the conclusion that although a significant percentage of TRD patients do respond to ECT, their clinical outcomes tend to be less favorable when compared to non-TRD patients.[81]

Another study, published in 2005, aligns with the findings mentioned earlier. It also indicates that for individuals with major depression, ECT is less likely to result in full recovery when the depression has shown resistance to medication or when it has been persistent over time. Interestingly, this study did not find that factors such as age or physical health significantly influenced the outcomes of ECT for depression.[82]

A similar conclusion was drawn in a multicenter cohort study published in 2023, involving 440 patients. This study found that as Treatment-Resistant Depression becomes more severe, the reduction in depressive symptoms with ECT becomes less significant. Additionally, they expressed concern about ECT being reserved as a last resort in the treatment of Major Depressive Disorder, as their findings indicated that lower levels of treatment resistance were associated with better ECT outcomes.[83]

In a recently published observational study from 2023, researchers assessed the response to Electroconvulsive Therapy in patients with Treatment-Resistant Depression compared to non-TRD patients, involving a total of 4244 patients. According to the Clinical Global Impression - Improvement Scale, the response rate to ECT was 65.9% in the TRD group, while it was 10% more in the non-TRD group. The study also identified that older age and more severe depression were predictive factors for a positive response in patients with TRD.

Additionally, the study's authors concluded that the TRD group's response rate, although lower than that of non-TRD patients, was notably higher than the response rates observed in the Sequenced Treatment Alternatives to Relieve Depression study, in which treatment steps 3 and 4 each resulted in a response in less than 17% of patients.[84]

There are also studies that produced somewhat different findings. For instance, a 2002 study concluded that when success was defined as achieving at least a 50% reduction on a Depression scale (HRSD) after ECT, there was no significant difference between patients resistant to antidepressant medications and those who were not, meaning both groups had an equally good chance of improving with ECT. However, when they assessed full recovery, they observed a slightly lower chance of achieving this state among patients who were resistant, however this difference in full recovery rates wasn't large enough to be statistically significant. The variance in findings from this study could be attributed to its relatively small sample size. [85]

In conclusion, it can be affirmed that while most studies indicate better outcomes for non-TRD patients, ECT remains effective for individuals with TRD and can be a valuable treatment option.

5.2.2.2 Repetitive transcranial magnetic stimulation (rTMS)

Repetitive transcranial magnetic stimulation is a secure and non-invasive therapeutic method employed in the management of various psychiatric and neurological conditions.[86]

A commonly accepted explanation for the enduring effects of rTMS on the brain is its ability to modify synaptic plasticity.[87]

rTMS has demonstrated its efficacy in treating depression and compared to electroconvulsive therapy, repetitive transcranial magnetic stimulation is considered to have fewer adverse effects, such as the absence of anesthetic risks, memory alterations, and reduced social stigma.[88]

A recent (2023) comprehensive systematic literature review involving 1,405 patients reveals that in the case of Treatment-Resistant Depression, the use of rTMS as an adjunctive treatment significantly increases the chances of achieving both a response and remission compared to pharmacotherapy alone.[89]

This finding aligns with other meta-analyses, such as a SLR conducted in 2014, which similarly concluded that augmentative rTMS was more effective than a sham treatment.[90]

Another systematic literature review further supports the idea that repetitive Transcranial Magnetic Stimulation is useful for TRD patients and concluded that it is significantly more effective than a sham for treating Treatment-Resistant Depression. rTMS resulted in a significant reduction in depressive severity, an increased likelihood of positive response, and a greater chance of achieving remission. Nevertheless, this review couldn't definitively determine the duration of these benefits.[91]

When comparing rTMS to ECT, a 2016 systematic review and meta-analysis of randomized controlled trials examining repetitive transcranial magnetic stimulation for Treatment-Resistant Depression, found that ECT is more efficacious in treating patients with TRD when compared to rTMS. Although rTMS did demonstrate a modest short-term improvement in depression symptoms compared to a sham, the evidence suggested that this effect might not be maintained over extended periods.[92]

While not limited to Treatment-Resistant Depression patients, a systematic literature review comparing electroconvulsive therapy to repetitive transcranial magnetic stimulation for Major Depressive Disorder found similar results. According to this review, ECT appeared to be slightly more effective than rTMS, however this variance did not reach statistical significance. Additionally, the review noted that rTMS, particularly right-sided rTMS (R-rTMS), was better tolerated. In essence, ECT might be slightly more effective but has more side effects, while R-rTMS is easier for patients to tolerate.[93]

In conclusion, the use of repetitive transcranial magnetic stimulation in patients with TRD offers a promising avenue of treatment. Multiple studies and systematic reviews suggest that rTMS can be effective in alleviating depressive symptoms in TRD patients. While it may not surpass electroconvulsive therapy in terms of overall efficacy, it often presents a more tolerable and acceptable treatment option with fewer side effects. However, it's important to note that the duration of rTMS benefits and the specific protocols that yield the best results require further investigation.

5.2.2.3 Deep brain stimulation (DBS)

Deep brain stimulation is utilized for a range of medical conditions, including TRD, but its precise mechanism remains a mystery. The therapeutic effects hinge on several factors such as the intensity and timing of electrical signals and the function of brain cells. Research indicates that DBS can increase the activity of the specific neurons it targets, but more research is necessary to fully understand the mechanism.[94]

In a systematic literature review and meta-analysis published in 2017, 14 studies were examined. These studies investigated the efficacy of Deep Brain Stimulation in the treatment of Treatment-Resistant Depression by targeting four distinct brain regions: The Subcallosal Cingulate Gyrus, Ventral Capsule, Medial Forebrain Bundle, and Nucleus Accumbens. The findings of this analysis revealed a significant reduction in Hamilton Depression Rating Scale (HDRS) scores when DBS was applied to these specific brain regions. Moreover, the study demonstrated the effectiveness of DBS in alleviating depression symptoms, with noteworthy response rates evident at multiple time intervals—1, 3, 6, and 12 months following the DBS treatment. However, it's important to note that the study also highlighted the occurrence of adverse events associated with the DBS treatment, particularly in relation to the targeted brain regions.[95]

Those results aligned with a previous systematic literature review from 2014, which also investigated the use of DBS targeting the subgenual cingulate cortex for the treatment of TRD. They concluded that it is associated with significant response and remission rates in patients with Treatment-Resistant Depression, observed both in the short term and over the medium to long term. However, the authors emphasized that these findings are preliminary and underscored the need for future controlled trials to further investigate this treatment.[96]

Several other and more recent systematic literature reviews have concurred with this conclusion, affirming that while Deep Brain Stimulation (DBS) shows promise, further research is necessary.[97,98]

5.2.3 Other emerging interventions

In addition to more traditional treatments and the mentioned brain stimulation methods, TRD management is exploring new approaches. This section will look at three different methods: Transcranial Direct Current Stimulation (tDCS), Vagus Nerve Stimulation (VNS), and Light Therapy. These new therapies offer potential ways to address TRD, which may improve outcomes for patients who haven't responded to other treatments.

5.2.3.1 Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation (tDCS) involves the administration of a mild and continuous electrical current through electrodes placed on the scalp, affecting the cerebral cortex.[99] Regarding the mechanism of action from a biochemical perspective, anodal stimulation appears to enhance excitatory synaptic transmissions, potentially promoting glutamate transmission while suppressing GABA transmission within the cortex.

Consequently, tDCS may exert both positive and negative regulatory effects on neurotransmitters such as dopamine, serotonin, and acetylcholine. These neural processes can potentially shift the balance between excitatory and inhibitory inputs, allowing anodal stimulation to modulate the activity levels of various neural network systems.[100]

The application of tDCS in treating TRD remains a subject of debate. A study conducted in 2012, involving 22 patients, reported that there was no significant difference in depression scores after 14 days when comparing anodal tDCS to sham tDCS. However, this study did reveal a positive impact of tDCS on secondary outcome measures related to emotions. So, the conclusion drawn, was the need for further extensive research in this area.[101]

In another study, which was a randomized double-blind sham-controlled trial published in 2012, it was found that a particular tDCS configuration, involving anodal stimulation applied to the left dorsolateral prefrontal cortex (DLPFC) and cathodal stimulation to the right DLPFC, did not exhibit effectiveness in treating Treatment-Resistant Depression. However, the study acknowledged several methodological limitations that should be considered when interpreting the results and they also emphasized the need for ongoing controlled studies.[102]

In a 2019 pilot study involving 18 patients with a focus on Treatment-Resistant Depression, transcranial direct-current stimulation was administered using specific electrode placements and parameters. The findings of the study revealed a favorable impact of tDCS on depressive symptoms and certain cognitive functions, albeit with varying responses among individuals. Notably, tDCS was well-tolerated and preferred by the majority of patients over other treatment options. Interestingly, the study suggested a potential delay in the onset of tDCS effects, shedding light on why some prior studies failed to detect differences between sham tDCS and actual tDCS interventions, possibly due to the need for longer follow-up periods. Nevertheless, it's important to acknowledge several limitations of this study, including its modest sample size and open-label design.[103]

In summary, the use of transcranial direct current stimulation for treating Treatment-Resistant Depression is an area that needs further investigation. While the existing research is still relatively limited, there are indications that tDCS holds promise as a potential treatment option for TRD. Further studies, with larger participant groups and possibly extended observation periods, are essential to clarify the potential benefits and limitations of tDCS in the treatment of TRD.

5.2.3.2 Vagus nerve stimulation (VNS)

VNS takes a foundational approach to influence the neural networks associated with depression. It achieves this by initiating stimulation in the vagal afferent fibers located in the neck. These convey impulses to specific regions in the brainstem, precisely affecting the locus ceruleus and dorsal raphe nucleus. VNS showed promising early sings of mood improvement in epilepsy patients, leading to the notion that it could be helpful in depression.[104]

In 2005, the FDA granted approval for VNS as an adjunctive long-term treatment for chronic and recurrent depression in individuals aged 18 and older.[105]

A recent 2020 meta-analysis, involving three controlled studies with 1048 Treatment-Resistant Depression patients, reveals that adjunctive Vagus Nerve Stimulation yields a higher response rate compared to the control group and also suggesting safety and tolerability benefits, including potential advantages during pregnancy. Additionally, the study concluded, that VNS may offer an advantage over certain other treatment options, such as electroconvulsive therapy, by avoiding neurocognitive side effects and anesthesia, making it a valuable consideration for individuals seeking alternatives in managing their TRD. Nevertheless, the authors warn against drawing firm conclusions due to the limited inclusion of randomized controlled trials and emphasize the necessity for additional studies to prove the positive effects of adjunctive VNS in treating Treatment-Resistant Depression. The authors also compared their results to another study published in 2019 involving 255 participants, that did not find significant antidepressant effects of VNS and concluded that the difference might be because the study included a type of electrical nerve stimulation on the ear which made the group of participants more varied.[106]

The authors of the 2019 study mention that due to the absence of data on suicide rates and the small sample sizes in the included studies, the review couldn't provide strong and definitive evidence of VNS efficacy for depression but they also conclude that more research is necessary.[107]

In the 2020 meta-analysis, a notable difference from the 2019 study was the assessment of study quality using the Jadad scale, which was identified as a potential factor contributing to the contradictory results.[108] In conclusion, for patients suffering from Treatment-Resistant Depression, Vagus Nerve Stimulation emerges as a potentially effective and well-tolerated adjunctive treatment option. While studies have shown promising results in terms of improved mood and response rates, caution is necessary due to limited randomized controlled trials and variations in study methodologies. Further research is needed to establish the precise efficacy and safety profile of Vagus Nerve Stimulation for TRD patients.

5.2.3.3 Light therapy

Light therapy refers to a non-drug approach which entails the everyday exposure to intense light though certain devices, like fluorescent light boxes. It is believed to stimulate specialized light cells in the retina, which then trigger the release of glutamate in the suprachiasmatic nucleus. However, the precise mechanism of action is not understood.[109]

Research indicates that Bright Light Therapy is likely effective not only for seasonal depression but also for depression in general.[110]

When examining the literature, it becomes evident that there is limited research specifically focused on patients with Treatment-Resistant Depression. One study addressing this issue involved 25 patients who completed a 3-week treatment regimen using Bright Light Therapy as an adjunct to psychopharmacotherapy. The study's findings revealed a statistically significant reduction in Hamilton Depression Rating Scale (HDRS) scores, indicating a positive effect of the treatment. Additionally, it was noted that the treatment was well-tolerated by the patients. However, the authors acknowledged that these results, while promising, are preliminary in nature. To establish the efficacy of BLT for TRD conclusively they add that further research is needed, specifically in larger patient samples, which should involve placebo-controlled, randomized, and double-blind clinical trials to provide more robust evidence of its effectiveness.[111]

In a recent pilot study published in 2021, researchers explored the combined use of Bright Light Therapy and Repetitive Transcranial Magnetic Stimulation for patients with Treatment-Resistant Depression. This study enrolled a total of 80 patients, and the findings indicated that this combined approach significantly enhances the antidepressant effect compared to using rTMS alone.[112]

Additionally, a study conducted in 2013 incorporated light therapy, specifically together with total sleep deprivation followed by sleep phase advance for three days, followed by five days of Bright Light Therapy alongside the patient´s drug treatment. The study's findings indicated significant improvement in depressive symptoms, both subjectively and objectively. Moreover, it was noteworthy that 8 out of the 13 patients sustained a positive response to the treatment. It is important to mention that the study had no placebo group and had a rather small sample size, however, the results do show promise.[113]

A study non-specific to TRD also demonstrated that the treatment is well tolerated[114], so in summary, it is worth considering the inclusion of light therapy as an adjunct or in combination with other treatment modalities when dealing with patients who have TRD since the studies showed that it indeed holds promise in enhancing the overall management of it.

6. Challenges and Future Directions

This chapter looks into the challenges and future directions of Treatment-Resistant Depression. It discusses treatment adherence and explores personalized medicine approaches. Additionally, existing research gaps and potential future directions that hold the key to advancing the understanding and treatment of TRD will be briefly looked at.

6.1 Treatment adherence

Within the current literature, it proves challenging to find specific studies addressing compliance in patients with Treatment-Resistant Depression. Consequently, the broader literature on compliance and depression in general will be drawn upon. A study from 1998 concluded that a noteworthy and substantial correlation exists between depression and noncompliance. It suggests that individuals suffering with depression are three times more prone to be noncompliant with medical treatment recommendations compared to non-depressed counterparts.[115]

In an article from 2003, it was noted that discontinuations commonly occur within the first month of therapy, and about 25% of patients fail to tell their physicians about stopping their antidepressant medication. The article emphasizes the important role of the physician-patient relationship, emphasizing that a good connection is a crucial factor in addressing non-compliance. A detailed explanation, covering expectations and potential side effects, is highlighted as a positive factor contributing to treatment adherence.[116]

In a recent 2022 meta-analysis addressing the challenge of treatment adherence in depression, researchers explored the effectiveness of interventions aimed at improving this issue. Their findings highlight the superiority of collaborative care employing a multi-professional approach compared to relying solely on primary healthcare teams. The study not only affirms the positive impact of this approach on treatment adherence but also underscores its benefits for symptom management. Additionally, the meta-analysis recognizes the potential of technology-based interventions, such as computer support systems, in enhancing medication adherence. These promising results warrant further research to delve deeper into their efficacy. Importantly, the study emphasizes the existing gap in evidence concerning the effectiveness of long-term adherence interventions, signaling the need for future research endeavors to address this aspect comprehensively.[117] While the studies discussed may not be specifically focused on TRD, they provide valuable insights into addressing adherence challenges and suggest potential future directions, like in the realm of technology.

6.2 Personalized medicine approaches

Personalized medicine customizes interventions for diseases by considering individual profiles at molecular, physiological, environmental, and behavioral levels.[118]

Efforts to personalize depression treatment through pharmacogenetics, subtype identification, clinical staging, comparative trials, and outcome moderators have encountered significant challenges. These challenges stem from the complex interplay between genetic and environmental factors, the absence of clear-cut depression subtypes, limited supporting evidence for certain strategies, and the difficult task of conducting a large number of trials needed for meaningful comparative effectiveness.[119]

Diverging from the previously mentioned prediction methods an innovative approach relies on big data predictive analytic models. This approach aims to create formulas that predict how depression will respond to treatment. These formulas are built using information about symptoms and easily measurable clinical features gathered from previous studies. The goal is to establish a foundation for constructing predictive analytic clinical decision support models, which would help choose the best personalized treatment for each patient. Furthermore, these tools could also pinpoint specific groups of patients who might benefit from more precise and costly biomarker assessments. The findings show that around twenty baseline variables from medical or patient reports reliably predict how well treatments work for MDD. These factors are good at predicting the overall treatment results. Importantly, no previous studies have tried to make equations for treatment outcomes using all these predictors together. The study shows encouraging preliminary empirical results and points out recent improvements in statistical methods, showing the potential for creating models that can provide helpful guidance in choosing personalized treatments for MDD. In summary, the study recommends collaborative efforts to set up a structured process for gathering information on well-established predictors of treatment response in extensive observational treatment studies.[120]

Other studies also picked the big data predictive analytic models like a study from 2018 that aimed to investigate the prognosis of depression by looking at various things like a person's clinical, psychological, and biological details over a 2-year period with a total of 804 patients. The study found that when it comes to predicting how depression unfolds for individual patients, the severity of their depressive symptoms is the most reliable predictor. They considered various factors like psychological, biological, and clinical aspects but found that none of them significantly improved the accuracy of predictions beyond what could be determined based on self-reported depressive symptoms alone.

However, even the most refined model they developed had only moderate predictive accuracy, indicating that more refinement is needed before such prediction models can be practically useful in clinical settings.[121]

The studies underscore the difficulty in developing precise and reliable models to guide treatment decisions for individuals with depression and while the studies discussed may not be specific to Treatment-Resistant Depression patients, they provide valuable insights into the general principles of personalizing treatment approaches. This knowledge can then be applied to TRD-specific patients, offering a foundation for developing personalized approaches to address the unique challenges associated with it. All in all, it can be said that further studies with larger groups of patients are necessary to enhance the generalizability of such approaches.

6.3 Research gaps and future directions

The thesis highlights crucial points, emphasizing the need to address research gaps, particularly in establishing a consensus on defining Treatment-Resistant Depression. The absence of unanimity poses challenges for studies, leading to uncertainties about whom to include when referring to TRD. A universal definition across countries could mitigate these challenges by providing a clear guideline for the inclusion of subjects in studies as well as simplifying the identification and categorization of TRD patients.

A 2021 article underscores the substantial gaps in comprehending and addressing TRD within the current healthcare framework. According to the article the gaps extend from delays in initiating antidepressant treatment to restricted access to psychological therapies and the prompt implementation of medication changes or adjunctive treatments. Furthermore, challenges in accessing secondary care are identified as a potential obstacle. The importance of TRD patients and their caregivers being cognizant of these gaps is emphasized. Recognizing and advocating for improvements in these critical areas, as outlined in the article, holds the potential to enhance the effectiveness and personalization of TRD management in the future.[122]

A cross-sectional survey from 2022 examining Treatment-Resistant Depression in Germany, France, and the UK revealed outcomes similar to those discussed in the previous study, highlighting the severity and challenges associated with TRD. Notably, a substantial portion of TRD patients received inadequate treatment through monotherapy, in contrast to prevailing guidelines advocating for combination or augmentation therapies and the low utilization of psychological therapy is also emphasized.

The results align with the findings from the earlier-discussed study. Furthermore, the study underscores the importance for a comprehensive, patient-centered approach to enhance treatment outcomes and address systemic barriers in healthcare delivery also akin to the aforementioned study.[123]

The recent articles on Treatment-Resistant Depression underscore the persistent challenges in defining and managing TRD. The identified gaps in treatment initiation and access to therapies remain prevalent issues. Given the recency of these findings, it is evident that these problems persist and require immediate attention and concerted efforts for future research and healthcare initiatives to improve TRD management.

7. Case report

Addressing Treatment-Resistant Depression in clinical settings is profoundly complex, and the process of finding the most effective treatment for each patient can be quite time-consuming., which will be shortly illustrated with a case example. The individual in question is a male in his twenties, with no known family history of psychiatric disorders and no somatic comorbidities, except for obesity. At the age of 13 the patient tried cannabis once, and by 16, he encountered his initial depressive episode marked by diminished drive, mood fluctuations, insomnia, and passive suicidal ideation. Rather than seeking psychiatric assistance, he reverted to cannabis, consuming it weekly for approximately a year. After three months into the first depressive episode, his symptoms reportedly improved, granting him a two-year respite from depression. However, at 18, the depressive symptoms returned and to this time he also experimented with other substances such as ecstasy, speed, and cocaine in an attempt to alleviate his depressive symptoms. His symptoms persisted, prompting him to seek psychiatric aid. He commenced psychotherapy at an outpatient facility, where he was prescribed 25mg of sertraline. Yet, after two months, there was no discernible improvement, leading to his hospitalization. During his hospital stay, he underwent treatment with venlafaxine (75mg) and mirtazapine (7.5mg). Following discharge, he adhered to this regimen for six months before discontinuing it. A period of six months ensued without depressive symptoms, only for them to resurface, leading to his first suicide attempt through overmedication with Pipamperon. Subsequent hospitalization saw him receiving risperidone (0.5mg), venlafaxine (150mg), aripiprazole (20mg), and lithium (1350mg) over seven months. Risperidone was phased out in favor of aripiprazole, alongside an increased dosage of venlafaxine (375mg). This combination proved efficacious, resulting in his discharge. However, several months later, he made another suicide attempt via lithium overdose,

prompting a brief rehospitalization before he and his parents opted for discharge against medical advice. A relatively stable three-month period ensued before a recurrence of depressive symptoms. Medication remained unchanged—venlafaxine (375mg), aripiprazole (20mg), lithium (1350mg)—with the addition of quetiapine retard (200mg, twice daily). After twelve months without symptoms, his condition worsened, prompting the initiation of lamotrigine at 50mg. Over time, the dosage was gradually increased to 100mg, resulting in an improvement in his condition.

The case demonstrates very well that it's often not as simple as initiating augmentation or combination therapy and achieving success. Instead, it frequently involves a process of trial and error, even after trying various treatments, success isn't guaranteed, necessitating the search for alternative approaches.

8. Conclusions

In conclusion, this master's thesis has delved into the complex landscape of Treatment-Resistant Depression, a challenging subset of depression where individuals do not respond adequately to traditional antidepressant treatments. The lack of a universal definition, coupled with variations in prevalence estimates, reflects the complexity of it. Future research should focus on establishing a universally accepted definition of Treatment- Resistant Depression, which could facilitate identification and categorization of patients across studies and healthcare settings. The exploration of different staging models and risk factors shows the need for a personalized and comprehensive approach to Treatment-Resistant Depression management. The review of pharmacological interventions points out the evolving nature of treatment strategies, including augmentation, combination therapy and antidepressant switching, each presenting unique considerations and potential benefits. Novel pharmacological approaches, such as ketamine, psilocybin, buprenorphine, and dextromethorphan, exhibit promise in alleviating depressive symptoms; however, continuous exploration is important for a better understanding of their role in addressing Treatment-Resistant Depression. The exploration of non-pharmacological treatment options, including psychotherapeutic modalities like cognitive behavioral therapy and dialectical behavioral therapy, has underscored their efficacy in Treatment-Resistant Depression management, with evidence supporting enhanced remission and response rates. Brain stimulation techniques, including Electroconvulsive Therapy, Repetitive Transcranial Magnetic Stimulation, and Deep Brain Stimulation, have emerged as promising alternatives to traditional medication-based interventions, again emphasizing the necessity for personalized and comprehensive

strategies in the management. Continued research is important to prove and optimize the efficacy of these treatments for Treatment-Resistant Depression. Other emerging interventions such as Transcranial Direct Current Stimulation, Vagus Nerve Stimulation, and Light Therapy, also revealed their potential in the management of Treatment-Resistant Depression. However, the validation of their effectiveness, safety, and overall role in the treatment also requires further investigation.

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