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Treatment-Resistant Depression: The Role of Electroconvulsive Therapy

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ABSTRACT

Introduction and purpose: Depression remains the leading cause of disability worldwide, affecting the lives of nearly 300 million people. A particularly severe form of depression is treatment-resistant depression (TRD), which is associated with significant health, social, and economic problems. Its prevalence varies due to the lack of a unified definition. This paper reviews the efficacy and safety of electroconvulsive therapy (ECT) in the treatment of TRD.

Material and methods: A comprehensive search of the PubMed database was conducted to identify studies published between 2015 and 2025 that focused on electroconvulsive therapy in the context of treatment-resistant depression. The search strategy included keywords such as "electroconvulsive therapy," "treatment-resistant depression", "safety of electroconvulsive therapy.'' Relevant articles were reviewed and evaluated based on the reported outcomes and the authors' conclusions.

A brief description of the state of knowledge: Treatment-resistant depression (TRD) affects a great number of patients diagnosed with major depressive. Effective management of TRD requires appropriate pharmacotherapy, careful diagnostic evaluation and consideration of patient adherence. Electroconvulsive therapy (ECT) appears to be the most thoroughly researched and clinically effective method, particularly in severe cases and in populations at higher risk, such as older adults and pregnant women.

Conclusions: ECT remains one of the most effective treatment alternatives for TRD, especially in patients with severe symptoms or psychotic features. Choosing between these treatments

should be guided by clinical context, patient characteristics, and personal preferences. Equally important is the need to continue working on breaking the stigma around mental health conditions and ECT, by raising awareness, educating people, and ensuring everyone has equal access to safe and effective treatment.
Keywords: electroconvulsive therapy, ECT, treatment resistant depression, TRD

1. INTRODUCTION AND PURPOSE

Depression is currently the most common cause of disability worldwide and is estimated to affect nearly 300 million people. One particularly severe and difficult form of the disorder is treatment-resistant depression (TRD), which is associated with serious health, social, and economic consequences [1]. TRD affects patients diagnosed with major depressive disorder (MDD), and its prevalence is estimated to range from 6% to 55% among patients with this diagnosis. This wide range results from the lack of a unified, widely accepted definition. Establishing consistent diagnostic criteria would allow for earlier identification of TRD, the implementation of uniform procedure algorithms, and better prediction of treatment outcomes [2].

This paper focuses on the use of electroconvulsive therapy (ECT) in the treatment of treatment-resistant depression. The history of ECT dates to 1938, when two Italian psychiatrists developed and patented the method. However, some historical sources suggest that the first ECT procedure may have been performed even earlier, with early experiments possibly taking place as far back as the 19th century. Despite over 80 years of clinical use, ECT continues to raise controversy [3].

The present study includes a literature review on the antidepressant effects of electroconvulsive therapy in the treatment of TRD, with a particular focus on its safety and potential side effects.

2. MATERIALS AND METHODS

To gather current scientific data, a literature review was conducted using the PubMed database, covering studies published between 2015 and 2025. The search strategy included the following keywords such as “electroconvulsive therapy,” “treatment-resistant depression,” “safety of electroconvulsive therapy.” Articles were included if the full text was available in either English or Polish. Inaccessible publications were excluded from the analysis. The selected studies were evaluated based on the presented outcomes and the conclusions drawn by the authors. The aim of the review was to provide a reliable overview of the efficiency and safety of electroconvulsive therapy in the context of treatment-resistant depression.

3. A BRIEF OF A STATE OF KNOWLEDGE

3.1 Definition and diagnostic criteria of TRD

The definition of treatment-resistant depression (TRD) is based on three main elements: an accurate diagnosis, adequate treatment, and a lack of therapeutic response [3]. So far, the most common diagnostic criterion for TRD is the lack of symptom remission—defined as at least a 50% reduction in symptom severity—despite two trials of antidepressant treatment using drugs from different pharmacological classes. To properly assess the effectiveness of treatment, the following factors are essential: adequate dosing, sufficient duration of pharmacotherapy, and appropriate cooperation between patient and the doctor (adherence) [1]. This criterion appears in more than 50% of TRD definitions; however, it is still insufficient to specify the optimal treatment duration or to standardize the definition of treatment failure—both of which are necessary for effective TRD treatment. Based on this criterion, it is estimated that TRD occurs in approximately 30% of patients diagnosed with major depressive disorder (MDD) [4].

3.2 Treatment-resistant depression and diagnostic errors

Effective treatment of treatment-resistant depression (TRD) requires prior exclusion of pseudo-resistance, which may result from misdiagnosis of mood disorders or inappropriate pharmacotherapy [5].

A major depressive disorder (MDD) is often misidentified as an episode of depression within the course of bipolar disorder (BD). Studies indicate that each year, the diagnosis changes from MDD to BD in 1–3% of initially diagnosed patients. In clinical case, making an accurate diagnosis between MDD and BD during a depressive episode is extremely challenging, as the differences can be subtle and difficult to detect, particularly when there is no comprehensive history including states of elevated mood. Moreover, patients often perceive hypomanic states as a normal improvement in well-being after depression and therefore do not report them to

their doctor. Diagnostic tools designed to assess depressive symptoms and support clinical evaluation, such as the Hamilton Depression Rating Scale (HAM-D) or the Patient Health Questionnaire (PHQ-9), may assist in differentiating between these disorders. Misdiagnosis carries serious consequences for patients with BD, including inadequate treatment that can lead to serious side effects such as switching to a maniac episode or increased risk of suicide [6].

Pseudo-resistance may also result from inadequate antidepressant treatment prescribed by a psychiatrist, or from failure to follow recommendations by the patient (non-adherence) which may affect as many as 20–50% of patients taking antidepressants. According to various sources, 40–70% of patients stop therapy ahead of time, and approximately 20–40% of patients adjust the medication dosage on their own [2]. The treatment for TRD should be preceded by a thorough analysis of the reasons behind treatment failure, particularly regarding diagnostic accuracy, pharmacological strategy, and patient's adherence. The minimum therapeutic trial duration necessary to determine lack of efficiency is typically 4–6 weeks of using the antidepressant in therapeutic doses. Additional factors that may contribute to treatment failure include psychosocial circumstances that maintain depressive symptoms—such as major life stressors or unresolved emotional states requiring adaptation [7].

Another source of diagnostic error leading to an incorrect TRD recognition is the failure to account for somatic conditions such as hypothyroidism, vitamin deficiencies, or tumor, as well as psychiatric misdiagnosis—which may affect up to half of patients diagnosed with major depressive disorder (MDD) [8].

3.3 Pharmacological strategies in the management of TRD

After excluding pseudo-resistance, the next step in managing treatment-resistant depression is the optimization of the current pharmacological approach. This includes increasing the antidepressant dose to the maximum that can be tolerated by the patient and maintaining it for a minimum of 4 to 6 weeks, then the clinical condition is assessed. In case of failure, switching to another antidepressant is recommended, then adding a second antidepressant from a different group (combined treatment), and augmentation, which involves adding a substance outside the class of antidepressants [9].

Switching strategies can be applied both within the same pharmacological class or between different classes. The main categories of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) [10].

The STAR*D study (Sequenced Treatment Alternatives to Relieve Depression) demonstrated that approximately 20% of patients with treatment-resistant depression achieved remission following a switching strategy.

Combination therapy involves the use of two antidepressants with different mechanisms of action. Commonly used combinations include mirtazapine or trazodone with an SSRI or SNRI. Although reports remain partially inconsistent, available data suggest that combination therapy may be more effective than monotherapy. Clinical trials have shown a symptom reduction of approximately 44–50% compared to placebo groups receiving SSRI alone. There is also evidence indicating favorable clinical outcomes with the combination of bupropion and either SSRIs or SNRIs [1].

The most used and best-documented strategy in TRD treatment is augmentation—enhancing the effect of antidepressants with agents outside the antidepressant class. These may include lithium, lamotrigine, or second-generation antipsychotics such as aripiprazole, quetiapine, risperidone, and olanzapine. More recently, ketamine has also been introduced as an augmentation agent [10].

3.4 Non-pharmacological strategies in the TRD treatment

In the treatment of treatment-resistant depression (TRD), non-pharmacological methods are also used, and the most important of them is the neuromodulation technique. The most commonly used are: electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), deep brain stimulation (DBS), and transcranial magnetic stimulation (TMS). Among these, TMS has a relatively low risk of adverse effects—both cognitive and somatic. However, it has not been shown to be more effective than ECT, which, as the oldest of the non-pharmacological methods, has the most thoroughly documented effectiveness in treating TRD [4].

3.5 Electroconvulsive therapy (ECT)

The history of electroconvulsive therapy has been controversial for decades. Nevertheless, current data clearly indicates that ECT is one of the safest treatments, is well tolerated by patients, and most importantly, it is an effective method of treating drug-resistant depression. Its clinical efficiency has been confirmed in numerous studies.

ECT involves the application of brief electrical impulses to the brain, inducing a short, generalized seizure. Each procedure is carried out under general anesthesia with the use of a muscle relaxant. A typical treatment cycle consists of 8 to 12 sessions, done two or three times per week [11].

Today, ECT is used in the treatment of severe depressive episodes, treatment-resistant depression, bipolar depression and mania, as well as in cases of treatment-resistant schizophrenia and catatonia. It is estimated that each year nearly 1.4 million patients worldwide undergo ECT, with TRD being the most common indication in industrialized countries [9].

3.6 Efficiency of electroconvulsive therapy

A meta-analysis of eighteen clinical trials comparing the effectiveness of electroconvulsive therapy (ECT) and pharmacological treatment in depression showed that ECT was significantly more effective than pharmacotherapy alone. Additionally, data collected by the Consortium for Research in ECT (CORE) indicate that the remission rate in patients with major depressive disorder (MDD) treated with ECT reached 80% [6]. In other randomized clinical trials concerning various indications for ECT, the remission rate was approximately 52%, while in large open-label studies it reached up to 75%. Obtained results are particularly important because, as previously mentioned, the most common indication for ECT is treatment-resistant depression (TRD) [9].

Despite the high efficiency, ECT is still frequently used only after multiple treatment failures. The practice of leaving the treatment with the fastest and most predictable effect as the last therapeutic option, is not observed in other fields of medicine. A study conducted in 2018 demonstrated that the greatest benefits in treating TRD were observed when ECT was introduced as early as possible after the diagnosis [11].

A study published in 2023 analyzed the relationship between the level of treatment resistance and the clinical effectiveness of ECT. Resistance was measured using the Dutch Measure for Treatment Resistance in Depression (DM-TRD). The study indicated that earlier use of ECT in patients with lower resistance levels, as defined by the DM-TRD scale, was associated with better clinical outcomes and a lower number of sessions. The authors suggested that the DM-TRD scale may become a useful tool which supports therapeutic decision-making and helps to predict treatment response to ECT in patients with TRD [12].

Electroconvulsive therapy (ECT) is considered to have a positive impact on the quality of life (QoL) of patients with treatment-resistant depression. During two years of observation, there were significant improvements in both physical and psychological QoL in 40–50% of patients. The most notable benefits were seen in patients who responded well to ECT, were married, had no disability, and experienced shorter depressive episodes. These findings highlight the durability of ECT's effects and its value in the long-term TRD treatment [13].

3.7 Suicide-related issues

A high percentage of patients with treatment-resistant depression report severe suicidal thoughts or tendencies. A retrospective cohort study conducted in 2020 showed a major reduction of suicidal ideation after nearly one week of treatment, which is just two or three ECT sessions. After completing a full cycle of ECT, remission of suicidal symptoms was achieved in up to 80% of patients who initially presented with high levels of suicidal ideation, assessed using the Hamilton Depression Rating Scale (HAM-D) [6].

Due to the extremely quick improvement in clinical condition of patients, electroconvulsive therapy can be considered as an effective intervention in life-threatening situations. In cases where therapeutic effect is required as soon as possible, ECT surpasses pharmacological treatment, which requires several weeks to become effective. Furthermore, according to some studies, ECT may be used in continuation therapy reducing the risk of relapse of depression in patients who have already achieved clinical remission [14].

3.8 Safety of electroconvulsive therapy

In 2018, the U.S. Food and Drug Administration (FDA) conducted a comprehensive review of electroconvulsive therapy (ECT) and found it both safe and effective. It also concluded that no further clinical trials are required for the use of ECT in the treatment of major depressive episodes—including treatment-resistant depression (TRD)—as well as catatonia. However, the FDA recommended the clinical research to be continued for the use of ECT in schizophrenia and mania, even though ECT is used globally for all these indications [9].

Electroconvulsive therapy is regarded as a safe procedure. Research confirms its safe use not only in the general population but also in specific groups such as pregnant women and older adults. The risks associated with ECT are comparable to those of other medical procedures that require general anesthesia. Deaths related to ECT are extremely rare, with an estimated mortality rate of 2.1 per 100,000 treatments. Available studies indicate that most complications and fatalities are related to already existing cardiovascular conditions in patients [15].

A study conducted in Poland in 2022, showed electroconvulsive therapy (ECT) as a safe treatment in patients over 65 years old. These findings are compatible with data from previous international research, reinforcing the safety of this treatment in older populations. Notably, adverse effects were reported in 47.7% of patients; however, a great majority of these (88%) were mild in intensity and resolved spontaneously without requiring additional intervention. What is particularly notable is that the treatment was well tolerated even among elderly patients with multiple somatic comorbidities — a group which is often considered at higher risk. Due

to this observation there is more evidence suggesting that age and physical health should not be considered as absolute contraindications to ECT. While the procedure, like any intervention involving general anesthesia, carries inherent risks, its safety remains highly favorable when performed under proper clinical supervision [16].

Electroconvulsive therapy (ECT) is increasingly recognized as a reasonable and relatively safe option for severe depression during pregnancy, particularly when other methods were ineffective. A review of 130 cases found that most adverse effects, such as transient fetal arrhythmias, mild uterine contractions, or preterm labor, were not life-threatening and did not require medical intervention [17]. Recent systematic reviews support these findings: four out of five stated that ECT can be safe during pregnancy, if it is done with appropriate precautions . Only one review advised more conservative use, suggesting ECT should be used in critical cases due to uncertainties concerning fetal risk [18]. The growing use of interdisciplinary protocols—including fetal monitoring, careful anesthetic selection, and collaborative care—helped to make ECT a viable and well-tolerated option for pregnant patients who need effective treatment [17].

3.9 Adverse effects of electroconvulsive therapy

The most common side effects of electroconvulsive therapy (ECT) involve cognitive functioning, although they are typically transient and reversible [19]. Shortly after treatment, patients often report difficulties with attention, short-term memory, and verbal fluency, which was confirmed by both neuropsychological testing and subjective accounts [20].

Particular attention has been paid to autobiographical memory deficits, which, unlike other cognitive effects, may last for several months after treatment. Importantly, these impairments do not correlate with clinical improvement or other demographic or clinical elements, suggesting that it is independent from the course of depression [21].

Less often, patients experience transient disorientation, headaches, nausea, and drowsiness after ECT sessions, especially among older people or patients receiving bilateral electrode placement over extended treatment courses [19]. Some patients also report problems with concentration and a sense of detachment immediately after the treatment [20].

While most side effects are mild and temporary, autobiographical memory impairment is considered the most significant and persistent cognitive consequence of ECT [21]. Its intensity is influenced by several elements, which include pulse width (ultra brief vs. standard), electrode placement (unilateral vs. bilateral), total number of sessions, and individual cognitive vulnerability [19, 21].

3.9 ECT vs. Ketamine: comparison

Both ECT and ketamine are effective therapeutic options for treatment-resistant depression (TRD), although they are both significantly different in their mechanism of action, onset of effect, safety, and clinical context in which they are best used. The ELEKT-D trial found that ketamine was more effective among outpatients with moderate to severe depression, while ECT brought better outcomes in hospitalized patients experiencing very severe symptoms [22].

A meta-analysis of six randomized trials further confirmed the general higher efficiency of ECT, particularly in cases of severe depression and in inpatient settings. Importantly, the side effect of both treatments also diverges. Ketamine was associated with fewer reports of headache and muscle pain, whereas ECT carried a lower risk of dizziness, visual disturbances, and derealization symptoms [23]. Notably, the ELEKT-D study also reported a lower treatment dropout rate in the ketamine group, suggesting that it may be better tolerated, especially among outpatients [22].

In summary, ECT remains the more effective option for patients with severe depressive episodes or psychotic features, whereas ketamine may be a preferred alternative for individuals treated in outpatient settings—particularly when rapid symptom relief and reduced cognitive side effects are clinical priorities [23]. These findings highlight the importance of personalized treatment planning and shared decision-making in managing TRD.

4. CONCLUSIONS

Treatment-resistant depression (TRD) remains one of the most challenging and emotionally burdensome disorders in psychiatry. Despite advancements in pharmacotherapy and neuromodulation techniques, a significant proportion of patients still fail to achieve adequate clinical improvement. In this context, electroconvulsive therapy (ECT), although often introduced only as a last-line treatment, consistently demonstrates high efficacy. Its ability to bring about rapid relief of depressive symptoms and sustain long-term remission has been confirmed in numerous studies. Importantly, current scientific data also confirm the safety of ECT in high-risk groups such as older adults and pregnant women.

Naturally, ECT carries the risk of adverse effects, primarily related to cognitive function; however, when modern procedural parameters are used, these symptoms are most often transient and manageable. The emergence of ketamine as an alternative therapeutic option has expanded the range of treatment strategies, particularly for outpatients who require a rapid clinical response. Nevertheless, further studies are needed to better understand the long-term efficacy and safety of ketamine.

The decision between ECT and ketamine should be made on an individual basis, considering the patient's clinical profile, personal preferences, and treatment setting. As demonstrated in this review, ECT remains not only an effective but also an empathetic form of treatment for individuals suffering from the most severe forms of depression. Early implementation of this method—guided by consistent diagnostic criteria and informed decision-making—may meaningfully improve treatment outcomes and reduce patient suffering.

In this context, the need to raise awareness about depression and its treatment becomes particularly important. Unfortunately, mental illnesses are still stigmatized in our society, and ECT as a treatment method often evokes fear and misunderstanding. It is essential—both from a clinical perspective and to the great benefit of patients—that electroconvulsive therapy and mental health issues are more widely communicated to the public, so that psychiatric taboos may finally be broken.

Despite its turbulent history, electroconvulsive therapy remains a highly effective and safe psychiatric treatment, particularly in cases involving suicide risk and in the management of treatment-resistant depression, across all age groups and including pregnant patients. However, further prospective, multicenter studies are necessary to deepen our understanding of ECT's mechanisms of action, to move toward standardized treatment protocols, and to improve clinical outcomes.

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Author's contributions

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Methodology: MK, PZ;

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Investigation: MK, AJ, MP, KM;

Resources: MK;

Data curation: MK, MB, MP, KM, PZ, JM, TK, AJ, TK;

Writing - rough preparation: MK, MP, AC;

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