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Assessing the Efficacy of Methods for Treatment-Resistant Depression: A Review

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ABSTRACT

Electroconvulsive Therapy (ECT), Transcranial Magnetic Stimulation (TMS), and Esketamine have all been proven to be effective against treatment-resistant depression (TRD). However, it is still unclear which method of treatment is the most effective both in general and in specific populations of patients exhibiting certain traits (i.e. psychosis) or with varied severities of TRD. ECT is the oldest form of treatment and has been proven effective, though not without significant side effects. TMS has also been shown to be effective, but without the side effects of ECT. Esketamine is the newest form of treatment for TRD, only having been approved by the FDA in 2019. Although current research demonstrates its efficacy, little research has been done on this modality because of its novelty. Trials from 2000-2019 were searched for and utilized to examine the efficacy of these three treatments in comparison to each other. The most recent and relevant studies were chosen. Studies completed before 2000 or utilizing patients without qualifying criteria for TRD were not included in our review. The data analyzed suggest that ECT is the most effective form of treatment overall, but TMS is noninferior in nonpsychotic patients and esketamine is effective for patients with TRD and no other chronic comorbidities.

Introduction

Prevalence of Depression

Depression is a common mental health disorder, affecting approximately 5% of the adult population worldwide (WHO). Research has demonstrated that depression has a lifetime prevalence of about 8% to 12% and it has grown to become the leading cause of disability, affecting approximately 400 million people worldwide.[1] An estimated 8.3% of American adults experience at least one major depressive episode (MDE) in their lifetime, and 5.7% report an episode with severe impairment. This percentage is even higher with respect to adolescents with 14.7% reporting at least one MDE in 2021.[2]

The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies depression as having a a depressed mood or loss of interest or pleasure in almost all activities (anhedonia), as well as having at least four more of the following symptoms: significant change in appetite, sleep disturbance, psychomotor changes, tiredness and lower energy, self-worthlessness and excessive guilt, inability to think and concentrate, and suicidal ideation. In order to be classified as having severe depression, a person must show eight or nine of the nine symptoms. These symptoms must also be present every day for at least two weeks.

Motivation for Research

Although an estimated 14.5 million adults suffer from at least one MDE every year and only about 60% receive treatment.[2] The effects of depression are prevalent in every ethnicity, age group, and socioeconomic class. Several factors lead to increased rates of depression including gender, marital status, and age. Depression is about

two times more common in women than in men, it increases with rates of separation and divorce, and it has been shown to increase with age.[3] Increased rates of depression have also been linked to increased rates of homelessness, suicide, lower socioeconomic status, obesity, diabetes, and more.[4] Because there are so many possible causes and effects, studying depression can be incredibly complicated, and treating it often poses additional challenges.

Pathophysiology of Depression

The pathophysiology of depression is not entirely understood, though there have been multiple social, biological, and psychological factors associated with it. The monoamine hypothesis states that depression is caused by the imbalance of neurotransmitters, specifically the depletion of Dopamine (DA), Norepinephrine (NE), and Serotonin (5HT) (Figure 1). Each neurotransmitter plays a distinct role in depression.

The deficit of Dopamine (DA), for example, increases anhedonia, the decreased ability to experience pleasure.[5,6] This is because the DA system plays an important role in reward in the brain, and the depletion of dopamine stops the brain from experiencing reward, causing a person to cease seeking pleasurable experiences and responding to motivational stimuli.[5]

Norepinephrine (NE) neurons project to the limbic system, which is a major part of emotional regulation inthe brain.[7] Functional imaging studies of depressed suicide victims have shown decreased sensitivity and levels of α2A-adrenoceptors, a NE transporter, in the prefrontal cortex. This causes unregulated levels of NE in the prefrontal cortex and unregulated mood.

Serotonin (5-HT) is the most widely studied of these neurotransmitters in the context of depression. Like NE and DA, 5-HT also projects to the limbic system, and plays a major role in mood and stress regulation. Although low levels of these neurotransmitters are traditionally associated with depression, new research suggests that they might have no correlation to depression, refuting the monoamine hypothesis.[8,9] Still, the most common prescribed antidepressants, Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), are made based off the monoamine hypothesis. They have been known to have a significant response rate and they are often used as the first line of treatment for those with depression. These antidepressants aim to enhance neurotransmission of 5-HT and NE and their efficacy continues to support the monoamine hypothesis.

Other changes in neurotransmission have also been shown to have some effects related to depression such as that of glutamatergic neurotransmission, deficits in the neurotransmission of gamma-butyric acid. These, as well as other imbalances like reduced neurosteroid synthesis, acetylcholine imbalance, thyroxine abnormalities, abnormal circadian rhythms, weakened endogenous opioid function, and dysfunction of certain brain circuits and structures have been shown to be related to depression.[10]

Evidence also suggests that there may be a link between depression and hippocampal genesis. Studies have shown that patients with depression often have a smaller hippocampus than those without it.[11] This is likely linked to the deficiencies in these neurotransmitters, which inhibit the growth of neurons.

The hormone estrogen is also involved with depression and the treatment of it.[12–14] Studies of depression show higher blood concentrations of tumor necrosis factor (TNF)-α and interleukin (IL)-6, which suggest that inflammatory cytokines are associated with depression.[15]

Evidence also suggests that patients with depression have an overactive hypothalamic pituitary-adrenal axis, which has an effect similar to the neuroendocrine response to stress, in comparison to those without depression.[16] All of these different factors complicate the understanding and treatment of depression.

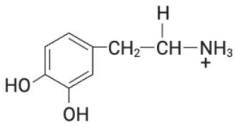
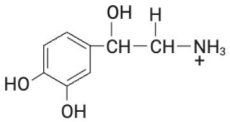
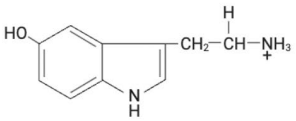
	Dopamine (DA)	Norepinephrine (NE)	Serotonin (5-HT)
			
Effects:	Reward and pleasure, motivation	Emotional regulation	Emotional and stress regulation
Structure:	Consists of a benzene ring with two hydroxyl side groups (catechol structure) with an ethyl chain attaching one amine group	Consists of a catechol unit and a hydrogen atom attached to the nitrogen molecule	Amino compound with 5-hydroxy substitution, an ethylamino arm attached to an indole ring (a benzene ring fused to a pyrrole ring)

Figure 1. Neurotransmitters Involved in Depression per Monoamine Hypothesis. Chemical structures of the three NTs involved in depression and their effects both in the non-depressed and depressed brain.[17]

Treatments of Depression and Treatment-Resistant Depression

Most depression is treated using some form of Selective Serotonin Reuptake Inhibitors (SSRIs) or Selective Norepinephrine Reuptake Inhibitors (SNRIs), antidepressants that aim to stop the reabsorption of serotonin and norepinephrine and raise the levels of those neurotransmitters in the brain. However, for about 30% of people, these antidepressants have little to no effect even after multiple trials of different medications. Those who are resistant to common antidepressants are classified as having treatment-resistant depression (TRD). The definition of TRD is not very clear as many researchers use various methods to determine and classify treatment-resistance, but it is generally accepted as having failed two drug trials. Treatment for TRD is limited and the average rate of remission for those with TRD is 15%.[18] Alternative treatments for this type of depression include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and less commonly, newer medications such as esketamine (Figure 2). These treatments vary in their effectiveness and side effects, which also vary by population.

	rTMS	ECT	(S)Ketamine
Function:	Uses magnetic field to create an electric pulse and depolarize cortical tissue to stimulate neurons	Uses electricity to alter concentrations of ions and electrical milieu to stimulate neurons	Binds to NMDA and other receptors to increase the level of glutamate in the brain
Effect:	Increases connection of DLPFC and limbic system and raises levels of DA, 5HT, and glutamate Promotes hippocampal neurogenesis and synaptic plasticity	Change volume of certain brain structures, induces neurogenesis, synaptogenesis, gliogenesis, regulates neurotransmission change blood flow and blood pressure	Blocks NMDA, opioid, monoaminergic and other receptors to increase the level of glutamate in the brain

Figure 2. Alternative Treatments for TRD

Functions of the Three Treatments Used for TRD and their Effects on the Depressed Brain.[18–25]

Electroconvulsive Therapy

ECT was first developed in the late 1930s as an alternative to the chemically-induced seizures that had been performed before, and was first used in hospitals in 1941. The use of seizures to manage psychiatric disorders was started based on an observation that patients with epilepsy had more glial cells, cells that modulate the rate of nerve signal transmissions and the synaptic uptake of neurotransmitters, than those with schizophrenia. Therefore, seizures were used to try to raise glial cell numbers to improve psychiatric illness. ECT uses stimulating electrodes attached to a patient's head to provide controlled electric currents, which cause a seizure. Other electrodes placed on the head record an EEG to monitor the seizure. The patient is also placed under anesthesia while the seizure is induced to prevent trauma and physical harm, as ECT without anesthesia is known to cause injury and post-traumatic stress disorder.[19] The procedure can be done unilaterally or bilaterally, but high-dose unilateral ECT is the preferred option due to patients having less cognitive side effects.[26] Along with TRD, ECT is used to treat manic episodes, catatonia, treatment-resistant schizophrenia, and severe bipolar and unipolar depression.

The underlying mechanisms of ECT are not entirely known, although there are several hypotheses about its effects. ECT uses electrical currents to alter the brain's concentration of ions and electrical environment to stimulate neurons.[27] This leads a group of stimulated neurons to fire simultaneously and cause a seizure. Generally, the seizure encompasses the cortex, sub-cortex, limbic system, basal ganglia, and thalamus, but the site of electrode placement and other variables can determine which areas of the brain are activated and which areas are more involved in the convulsions.[28] Studies show that ECT changes glucose metabolism and blood flow in the cerebrum, as well as raises blood pressure in the brain. The change in blood pressure can break the blood brain barrier, bringing certain chemicals in and changing the brain's micromilieu, although studies suggest this only occurs after multiple treatments of ECT.[29] During an ECT, other electrodes are placed on the patient's head to record an electroencephalography (EEG). The EEG has shown that after the application of ECT, delta activity (neural fluctuation within 0.5 to 4 Hz) in the prefrontal cortex and the waveform slowing can be used as a predictor of response.[30] For patients with psychotic depression, an increase in theta oscillations (4-7 Hz) was linked to a decrease in psychotic symptoms, and was overall associated with less psychotic adverse effects of ECT.[31] ECT is known to regulate neurotransmission and the release and reuptake of other neurochemicals, such as hormones and neurotransmission, including DA, NE, and 5HT.[20] ECT has also been reported to change volume in the brain's gray and white matter, as well as its structures, especially in the hippocampus, amygdala, and other areas involved in regulating mood. ECT is also able to cause synaptogenesis, neurogenesis, gliogenesis, angiogenesis, and dendritogenesis.[20]

Other neuroplastic effects of ECT include altered expression of targeted genes and improved connectivity of neurons in the hippocampus, although these findings have only been in experimental animals so far.[32,33]

ECT treatment is often completed two or three times a week for a total of six to twelve treatments. Because of the seizure and anesthesia requirements, this form of treatment has the greatest range and most significant side effects compared to the potential alternative treatments. Side effects can include headaches, nausea, dizziness, confusion, memory loss, and jaw and muscle ache. These side effects usually last for just a few minutes after the procedure, but in some rare cases, they can last for multiple days or even weeks.[34] Despite these instances where severe side effects last for longer than a few hours, ECT is overall considered a safe treatment for those with TRD. Although it has more severe side effects, ECT has been proven to be more effective for patients with more severe depression, and even more so for those with symptoms of psychosis.[35,36]

Transcranial Magnetic Stimulation

TMS, developed in the 1980s, uses a magnetic field to create a small electrical current pulse that runs through specific areas of the brain, stimulating peripheral neurons in a similar way to that of an electrical stimulation as in ECT. Unlike ECT, TMS is non-invasive and does not require the patient to be placed under anesthesia. It regulates neural functioning by inducing the electric field from the source of the voltage surrounding the short capacitor to reduce to zero, discharging an electrical current into a stimulated coil, generating the magnetic field. This causes the cell membranes of neurons' potentials to depolarize in the outer layer of brain tissue, changing the activity of those neurons.[21] This process can be altered through many factors, such as the frequency and intensity of the stimulation, the duration between pulses, the total number of pulses, and the different regions targeted by the stimulation. Studies show that high-frequency (>5 Hz) stimulation causes excitatory effects, while low-frequency (<1 Hz) causes inhibitory effects on the brain. rTMS is the type of TMS most often used to target psychological diseases. Like ECT, the exact mechanisms of TMS are not entirely known, but it is usually thought that rTMS has similar neuroplastic effects as ECT, and can change synaptic plasticity, including the function of the N-methyl-D-aspartate (NMDA) receptor.[22,23] rTMS also induces cortical oscillations in a similar way to ECT. rTMS has several reported antidepressant effects, including increasing the levels of DA, 5HT, and glutamate, an excitatory neurotransmitter important to cognition, memory, and mood regulation. rTMS has also been shown to increase neurotransmitter levels, it has been shown to alter neural circuits and brain networks. Studies suggest it increases the dorsolateral prefrontal cortex (DLPFC) and medial temporal limbic connectivity through hypoperfusion, and attribute its effects to its regulation of connectivity of the frontostriatal (pathways connecting frontal lobe regions with the basal ganglia) network.[24] It has also been suggested that rTMS induces hippocampal neurogenesis and synaptic plasticity, as well as promote IL-6 release.[21]

The rTMS procedure usually occurs three to five times a week for four to six weeks. TMS can also be used bilaterally and unilaterally, usually with low frequency stimulation of the left DLPFC and high frequency stimulation of the right DLPFC, or both. Bilateral treatment has also been shown to have higher response rates than unilateral.[37] In contrast, rTMS has a much better response rate for patients exhibiting more mild and moderate forms of depression, but research supporting its efficacy, especially long-term, is widely varied and disputed. Its side effects are also much more mild, mostly headaches and dizziness, although there have been reports of dissociation and seizures.[38]

Esketamine

Unlike the other two treatments, ketamine is a drug traditionally used for its anesthetic properties. Introduced over thirty years ago, it induces loss of consciousness, analgesia, amnesia, and immobility. Its place was never very important in clinical practice as significant side effects were reported for the drug, and other IV anesthetic drugs took what would have been its place. There are two types of ketamine: (S) ketamine and (R) ketamine, which come from the two isomers of 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone ketamine. Ketamine has multiple binding sites, such as NMDA and non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic, and opioid and monoaminergic receptors. It also has been found to interact with voltage-dependent ion channels, such as Na and L-type Ca channels. The NMDA receptor is known to be responsible for most of the amnestic, psychotomimetic, and analgesic properties of ketamine. Ketamine binds to NMDA to block the binding of the neurotransmitter glutamate therefore raising the level of glutamate in the brain. The (S) isomer has a higher affinity with the NMDA receptors, making it three to four times more analgesic potent than the (R) isomer.[39,40] Although the (S) isomer has more analgesic potency than the (R) isomer, when its performance is compared for TRD, the results are varied.[18,25]

In 2019, the FDA approved (S) ketamine, in the form of a nasal spray, for use specifically to treat TRD (Figure 3). (S) ketamine is expected to be just as effective as (R) ketamine, which is administered through IV, but much simpler to administer. Esketamine has anesthetic properties, so it has many similar side effects as general anesthesia, including headaches, nausea, dizziness, dissociation, vertigo, sedation, and dysgeusia. The

efficacy of esketamine compared to intravenous ketamine is not clear, as several studies have shown varied results for both.[41]

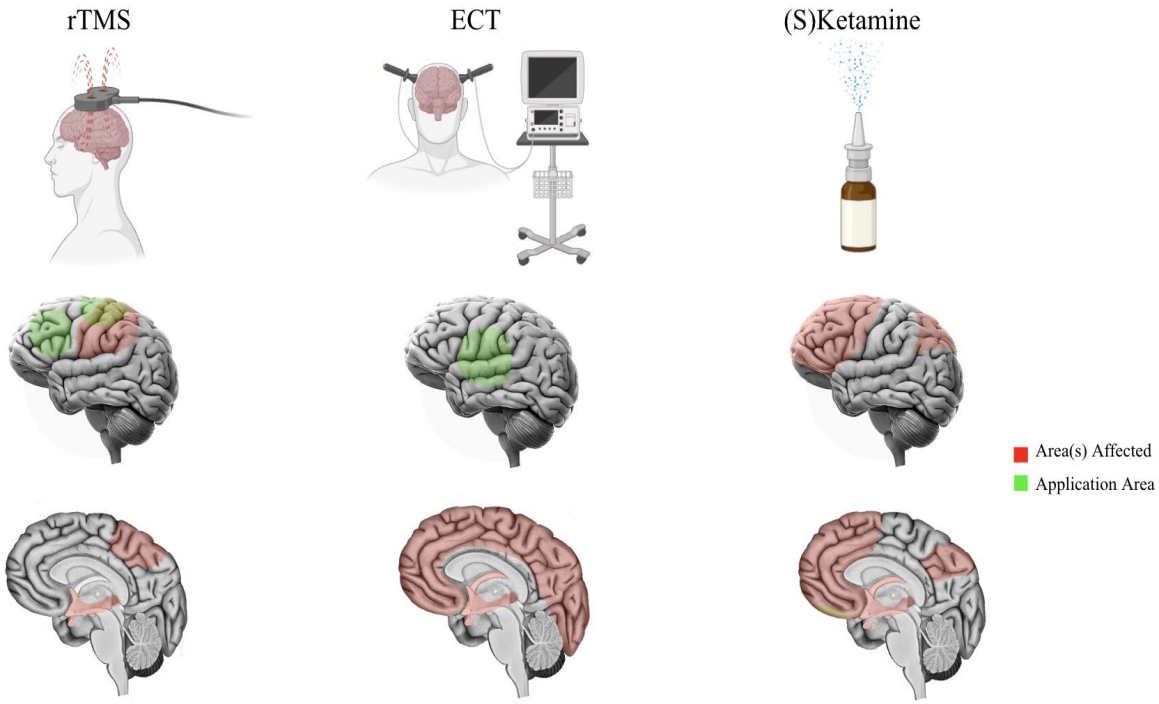


Figure 3. Treatments for TRD and Targeted Areas

rTMS: Administered to DLPFC and affects limbic system and hippocampus.
ECT: Administered to frontotemporal lobe and affects the entire brain
Esketamine: Administered through the nose and affects the prefrontal cortex and limbic system [42,43]

This paper aims to (1) understand the different methods of treating TRD (2) compare and contrast those methods (3) determine which form of treatment has the best outcomes according to response and remission rates for various groups of patients.

Methods

Study Selection

This systematic review and meta-analysis was done by conducting a systematic literature search in PubMed, the Cochrane Library, and Embase databases. Keywords included are depression, depressive disorder, MDD, treatment-resistant depression, electroconvulsive therapy, ECT, transcranial magnetic stimulation, TMS, ketamine, and esketamine.

Eligibility Criteria

Inclusion criteria: (1) subjects were depressed patients with a diagnosis meeting the Diagnostic and Statistical Manual of Mental Disorders (DSM), or the patient has moderate or severe depression (2) subjects meet some qualifying criteria for TRD (3) studies discussing ECT, TMS, or esketamine, (4) age ≥ 18, (5) uses depression rating scale as main outcome indicator. Exclusion criteria: (1) studies not discussing ECT, TMS, or ketamine, (2) studies that were conducted before 2000, (3) repeated published literature, (4) animal experiments, (5) studies with a large difference in indicators.

Abstracts and full texts of the literature were screened.

Data Extraction

To conduct the research, data was manually extracted from individual studies meeting inclusion and exclusion criteria. Data was manually inputted and conglomerated into a database for further analysis. The following information was extracted: author, publication year, study design, sample size, average age, duration of illness, clinical indicators, ECT parameters, MST parameters, duration for treatments, and test score standard deviation (SD).

Results

Study Selection and Study Characteristics

Initial Screenings Identified 23 papers from PubMed, the Cochrane Library, and Embase databases. After removing 1 duplicate publication, 4 systematic reviews and meta-analyses, and 6 irrelevant records, 12 were obtained. After reading the 12 articles, 11 were finally included in the meta analysis, including a total of 1,115 subjects.

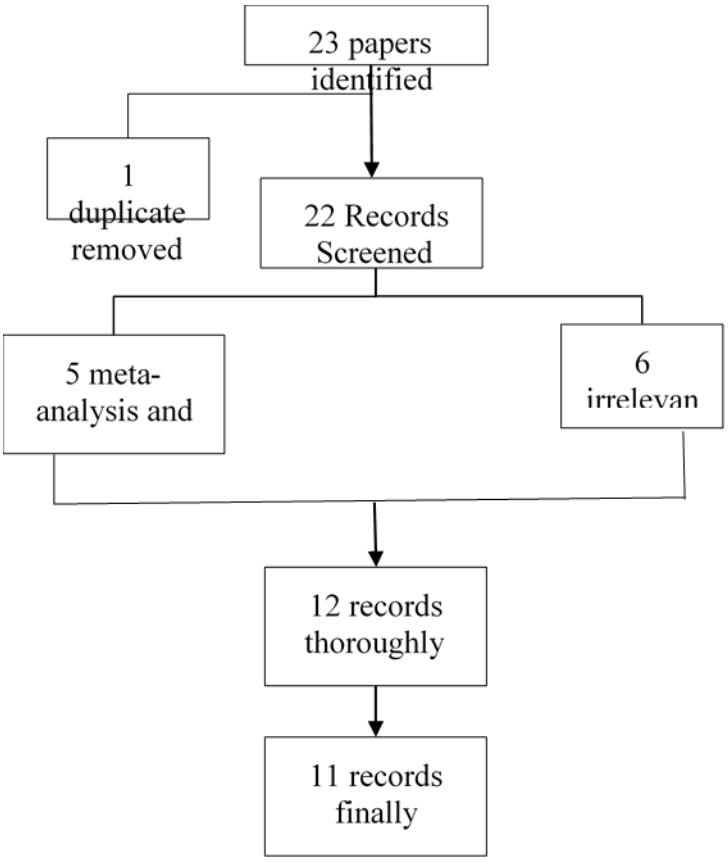


Figure 4. Process of Literature Screening

Among the 11 articles included, 7 were randomized controlled trials and 4 were non-randomized control trials. All tests had relatively complete results, and all studies reported a loss of subjects.

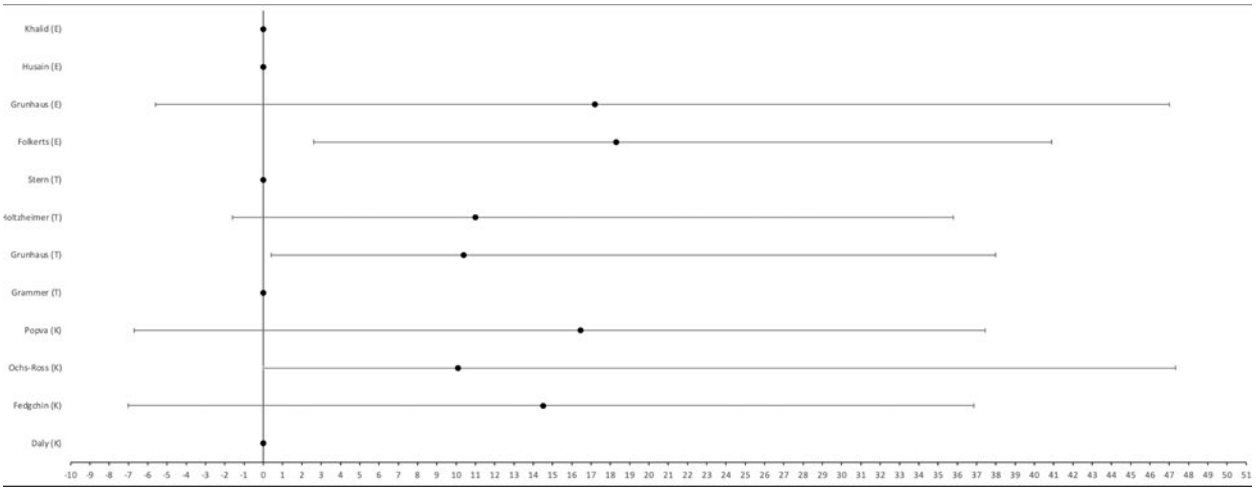


Figure 5. Forest Plot of Efficacy of TMS, ECT, and Esketamine

Efficacy of ECT

All four studies on ECT used the HAM-D rating scale to determine the efficacy of esketamine in treatment-resistant depression, and a total of 352 patients were included. In one study, antidepressants that patients had already been taking continued to be administered, and in the others there was a wash-out phase to stop all existing medications. The studies on ECT were relatively short, lasting from 2 to 4 weeks of treatment, or about 4 to 20 sessions. ECT was always done right unilaterally or bilaterally. Three studies specifically reported on the effects of ECT on psychotic and nonpsychotic major depression, with varying results. Two studies reported an increase in the efficacy of ECT for patients with psychosis, and one study did not report any difference between psychotic and nonpsychotic patients.

	Average Change in Score	Length of Treatment	# of Treatments	Mean Age (SD)	Location of Treatment	Response	Remission
Khalid et al., 2008	-12.05	--	4-13	53.3 (15.9)	Right Unilateral and Bilateral	65.8%	53.3%
Folkerts et al., 2007	-18.3 (5.1)	2 weeks	6	47.6 (14.7)	Right Unilateral	76.2%	--
Husain et al., 2004	--	3-4 weeks	2-20	56.2 (16.2)	Right Unilateral and Bilateral	79.1%	74.7%
Grunhaus et al., 2000	10.8 (9.3)	Up to 20 days	7-14	63.6 (15.0)	Right Unilateral and Bilateral	80%	--

Figure 6. Treatment Methods and Outcomes of Electroconvulsive Therapy

Table of four ECT trials from 2000-2008 showing average change in HAMD score, length of treatment, number of treatments, mean age and standard deviation, location of treatment, percent response, and percent remission after 2-8 weeks. Gaps in table are due to lack of information in studies used.[44–47]

Adverse Effects of ECT

One study reported adverse events. It reported a loss of 20 patients due to adverse events, the most common being confusion or memory problems.[46]

Efficacy of TMS

Three of the studies used HAM-D and one study used PHQ-9 to evaluate the efficacy of treating depression symptoms. A total of 140 patients were included in these studies. The length of studies ranged from two days to six weeks, with most targeting the left dorsolateral prefrontal cortex (DLPFC). One study included a bilateral treatment and varying frequencies on the left DLPFC, and another study tested several different placements and frequencies (high and low frequencies on the left DLPFC, and low frequency on the right DLPFC). Three studies tested TMS against a placebo, and one tested it against ECT. Compared to ECT, TMS performed worse in patients with psychotic depression, but was noninferior in patients with nonpsychotic depression. In one

study, it was determined that TMS performed better for patients with mild-to-moderate depression rather than those with severe depression.

	Average Change in Score	Length of Treatment	# of Treatments	Mean Age (SD)	Location of Treatment	Response	Remission
Grammar et al., 2015	--	4-6 weeks	20-30	41 (15.5)	Left DLPFC and bilaterally	Moderate: 55% Severe: 33%	Moderate: 60% Severe: 19%
Holtzheimer et al., 2010	-11 (3 wk)	2 days	15	Range: 20-74	Left DLPFC	3 wks: 36% 6wks: 36%	3 wks: 36% 6 wks: 29%
Stern et al., 2007	-40%	10 days	--	52.8 (10.3)	HF Left, LF Left, LF Right	60%	33.3% HFL 10% LFR
Grunhaus et al., 2000	-10.4 (7.3)	4 weeks	20	58.4 (15.7)	Left DLPFC	45%	--

HF/LF: High/Low frequency
DLPFC: Dorsolateral Prefrontal Cortex

Figure 7. Treatment Methods and Outcomes of Transcranial Magnetic Stimulation

Table of four TMS trials from 2000-2015 showing average change in HAMD score, length of treatment, number of treatments, mean age and standard deviation, location of treatment, percent response, and percent remission after 2-8 weeks. Gaps in table are due to lack of information in studies used.[47–50]

Adverse Events of TMS

Two studies reported adverse events: the first had one patient (7%) with increased suicidal ideation following treatment, and the second reported one patient needing to take analgesics as a result of severe headaches and nine others who had severe headaches that subsided within a few hours of TMS. There was no correlation found between headaches and antidepressant effects.[49,50]

Efficacy of Esketamine

All four studies on Esketamine used the MADRS rating scale to determine the efficacy of esketamine in treatment-resistant depression, and a total of 661 patients were included. Esketamine was taken adjunctive to an oral antidepressant in all studies. The MADRS scores were converted to HAM-D. Three studies had four weeks of treatment and one had 15 to 74 days of treatment. In all the studies, esketamine was administered twice a week through nasal spray. Every study compared the results of esketamine to a placebo, and one study specifically focused on elderly patients.

	Average Change in Score	Length of Treatment	# of Treatments	Mean Age (SD)	Response	Remission
Fedgchin et al., 2019	-14.5 (10.7)	4 weeks	8	46.3 (11.2)	--	53.6%
Popova et al., 2019	-16.5 (9.5)	4 weeks	8	Range: 18-64	69.3%	52.5%
Daly et al., 2018	28mg: -4.6 56mg: -6.4 84mg: -9.6	Up to 74 days	4-24	44.7 (10.0)	28mg: 38% 56mg: 36% 84mg: 50%	28mg: 13% 56mg: 27% 84mg: 40%
Ochs-Ross et al., 2000	-7.8 (9.8)	4 weeks	8	70.6 (4.8)	27%	17.5%

Figure 8. Treatment and Outcomes of Esketamine

Table of four Esketamine trials from 2000-2019 showing average change in HAMD score, length of treatment, number of treatments, mean age and standard deviation, location of treatment, percent response, and percent remission after 2-8 weeks. Gaps in table are due to lack of information in studies used. [51–54]

Adverse Events of Esketamine

All four studies reported adverse events. The first reported less than 20% of patients experiencing them, with the most common adverse events being nausea, dissociation, dizziness, vertigo, and headache.[51] The second reported 7% of patients receiving esketamine having an adverse event, with the most commonly reported ones being dissociation, nausea, vertigo, dysgeusia, and dizziness. This was much higher than the 0.9% of patients who experienced adverse events while taking the placebo with antidepressant.[54] Another reported a loss of 3 patients (5%) due to adverse events. These were syncope, headache, and dissociative syndrome. In the fourth study, 4 patients (5.6%) of patients discontinued the study due to adverse events. 51% reported experiencing adverse events, although most were mild to moderate and were resolved on the dosing day. The most common were dizziness, nausea, increased blood pressure, fatigue, and headache.[53]

Discussion

All four studies on ECT performed treatment unilaterally on the right side of the brain, and three also administered it bilaterally. Treatment lasted for two to four weeks, with two to twenty treatments. The response rate for ECT was the highest of all of the treatments, with every study reporting over 65% of patients responding. The remission rate was also the highest, with two studies reporting 53.3% and 74.7% of patients reaching remission. In ECT, there was no difference found for bilateral and unilateral treatment. Three of the studies switched from unilateral to bilateral administration if one was not as effective as preferred, but it was not reported and differences between various types were also not reported (Figure 6).

TMS was generally administered on the left DLPFC, although two studies also included the option to have it done bilaterally, and one tested various frequencies in the left DLPFC, as well as the right. Treatment

ranged from two days to six weeks, and 15 to 30 treatments. TMS was generally less effective than ECT, with its response rate being about 33% to 60%. Remission was reached in 10-60% of patients, with varying results based on the severity of patients' symptoms and the area in which the TMS was administered. Every study administered TMS to the left DLPFC, but one study also administered it bilaterally, and another recorded results for both the left and right DLPFC at various frequencies. The first study did not report differences between bilateral and unilateral TMS. The second study showed a clear preference for high frequency left DLPFC and low frequency right DLPFC treatment. Both of these groups achieved 60% response and had rates of remission at 33.3% and 10% respectively. This compares to the low frequency left DLPFC group, which had no remitters or responders (Figure 7).

All studies on esketamine administered it through a nasal spray and they were all coadministered with an oral antidepressant. Three studies' treatments lasted four weeks, with two treatments a week, and one lasted for 74 days and 4-24 treatments were administered. Esketamine had the largest range of response, with 27% to 69.3% responding. Likewise the rate of remission also had the largest range, with 13% to 53.6% reaching remission. One study on esketamine recorded differences in dosage. In the decrease of median scores, response rate, and remission rate, the higher dosage, 84mg, was consistently more effective than the lower dosage, 28mg. The mean decrease in scores were 9.6 and 4.6, the response rates were 50% and 38%, and the remission rates were 40% and 13%, respectively. One study on Esketamine reported specifically on elderly patients, and the mean age for that study was 70.6, about 20-30 years higher than the other three studies (Figure 8). The response and remission rates for this study was much lower than the other studies (about 30% lower), showing that esketamine is likely less effective for elderly patients, although more research should be done to confirm this result.

Previous authors have discussed that patients with psychotic symptoms generally respond better to ECT than those without. Our results section shows that this is mostly true. In two studies, patients who displayed symptoms of psychosis responded better to ECT. In the first, patients with remissions' mean HAM-D scores decreased by 23.1 for patients with psychosis and decreased by 11.6 for those without psychosis and the second stated that patients with psychotic symptoms have more remission than those without.[46,47] But, a third study did not find any significant difference between the presence or absence of psychotic symptoms in remitters and nonremitters, with 57% of remitters exhibiting psychotic symptoms and 53% of non remitters exhibiting psychotic symptoms.[44] Unlike ECT, previous authors have shown that TMS is more effective in patients with more mild and moderate depression, as well as those without psychotic symptoms.[48] The results section supported the previous studies. In one study, TMS was shown to have 41% higher remission in those with mild-to-moderate depression.[50] In another study, TMS was shown to be just as effective as ECT in nonpsychotic depression, with the mean decrease in HAM-D for ECT patients being 11.6 and 12.5 for TMS.[47] But, TMS was inferior for psychotic depression, with the mean decrease being 7.9. None of the studies on Esketamine reported anything on psychotic and nonpsychotic patients.

Unlike the difference in rates of response and remission for patients with and without psychotic symptoms, none of the studies reported any significant adverse effects, but every treatment modality did have some adverse effect associated with it. For ECT, one study reported a loss of 20 patients due to adverse events, with most of their adverse effects being confusion or memory loss.[46] For TMS, most of the adverse events were severe headaches that usually subsided within a few hours of treatment. In the studies of Esketamine, 7-51% of patients experienced adverse events and it is unclear whether or not this was influenced by dosage, age, or other factors. Most of these adverse events were mild symptoms such as nausea, dizziness, and headaches.

Conclusion

This review summarizes the results from 11 unique studies from 2000-2019. This work helps to understand the efficacy of different treatment modalities for TRD. Although our results indicate that ECT is most effective

overall, esketamine and TMS are not inferior in some cases. More research is required to confirm this result and better elucidate the underlying reasons for higher remission rates. While our review examines a larger sample size than any individual study, our question would still benefit from a systematic, large-scale study that compares the three different treatment modalities that accounts for concomitant treatments (i.e. SSRIs), demographic differences (i.e. larger percentage of women with TRD), and methods of delivering treatment (i.e. unilateral or bilateral ECT/TMS).

Limitations

There is a very limited number of studies comparing ECT, TMS, and Esketamine. One study comparing ECT and TMS was used, and the others were not comparative.[47] For ECT, some studies administered ECT at different frequencies. Three studies applied ECT both unilaterally on the right side and bilaterally, but one only administered right unilateral ECT. This makes it unclear whether or not right unilateral or bilateral ECT is superior for treatment-resistant depression. For TMS, various frequencies on the left and right cortexes were used. Some studies used bilateral TMS, as well as various frequencies on the left and right cortexes, not just the standard left DLPFC TMS. This could insinuate that a particular type of TMS is more effective than another due to the results of a particular study, and it wouldn't be known whether one treatment is more effective than another. In the studies for Esketamine, each study administered a different dose of esketamine. Some studies even administered multiple doses, but they weren't clear on the efficacy of each dosage, leaving it unclear whether or not higher or lower dosages of Esketamine are more effective. Esketamine is also a very new treatment, and a limited number of studies are available on it.

Similar to the ways in which the methods for the TRD studies had slight variations making it more difficult to compare and contrast efficacies, studies also used different rating scales to quantify depression severity and depression resolution. The studies used different rating scales like MADRS, PH-Q, and HAM-D. In order to compare studies, scores were all converted to HAM-D. Each of these rating scales are subjective surveys completed by the patient about their own systems. Although researchers have developed methods to convert scores and rating scales between each other, this limitation must still be acknowledged. The scoring systems each have different advantages and disadvantages based on their level of detail and patient subjectivity which makes a unilateral comparison challenging. Since we converted all depressing scales to HAM-D, our results may be skewed given the scale's known limited sensitivity and multidimensionality.

Studies were also inconsistent with concomitant treatments, with several allowing them and others requiring a washout of all concomitant treatments. This means that results of the studies are unclear as to whether or not patient's scores were changing due to their concomitant treatments or from the treatments provided, as some studies show that SSRIs take a long time to take effect, up to six weeks, so results could be due to the concomitant treatment rather than the treatment provided.

Many studies had a wide age range, and mean ages for the studies varied by almost thirty years. Because the ages of patients in treatments were not uniform, it is unclear whether their ages influenced the results of the studies, potentially making one treatment more or less effective than another for that particular age range, as previous studies have shown that some studies, like ECT, are more effective for older patients. Some treatments are more effective for patients who are older or younger, and without clear results on different age groups, it is hard to say whether or not results are due to the patient's age or some other factor. In every study but one, there were more females than males enrolled. This could mean that the results are skewed toward female patients, as they could respond differently to a treatment than males. However, more women have TRD than men, so the results do accurately represent the population with TRD.[55]

Most of the studies reported remission rates, but for every study, the score needed for remission would still be classified as mild depression. This could mean that many of the patients who achieved remission still have mild depressive symptoms, even after they have been treated for TRD. These results make it so that it's

unclear whether or not the treatments allow patients to achieve full remission, as in they no longer have depression, or if their depression has just gotten much more mild. Most of the studies used did not study long term effects of the treatment, with the longest study continuing for only 74 days.

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