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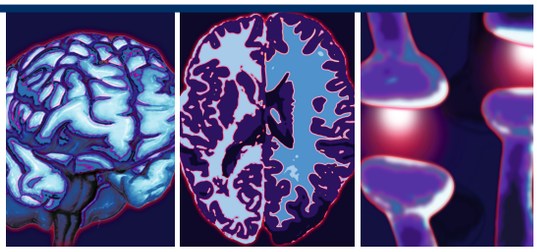

Clinical applications of electroconvulsive therapy and transcranial magnetic stimulation for the treatment of major depressive disorder: a critical review

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Practice points

- Major depressive disorder (MDD) is a common psychiatric illness that significantly impacts quality of life and is a leading cause of disability worldwide.
- Many patients do not obtain adequate relief of depressive symptoms from antidepressant medications alone.
- Neurostimulation options, such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation, are currently available for the treatment of MDD.
- To date, ECT is a safe and highly effective form of treatment for many psychiatric illnesses, including MDD.
- The routine clinical use of anesthetic agents, muscle relaxants and optimal stimulation parameters have significantly increased the safety and tolerability of ECT.
- The rate of depressive symptom relapse following a successful acute course of ECT is high, warranting the use of continuation therapies.
- Transcranial magnetic stimulation is well tolerated and performed in an outpatient setting.
- Additional research needs to be performed to further optimize somatic therapies for the treatment of MDD.

SUMMARY Depression is a common and debilitating psychiatric disorder that is often unable to be effectively treated with pharmacotherapeutic agents alone. Electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) are among several somatic therapies available for the treatment of major depression. The purpose of this article is to synthesize current information on ECT and repetitive TMS as treatments for pharmacotherapy-resistant major depression regarding its use in neuropsychiatric clinical practice. The current psychiatric literature indicates that both ECT and TMS are effective antidepressant treatments. ECT is a safe and highly effective treatment for depression. The literature also illustrates that TMS has a favorable side-effect profile, excellent tolerability and modest efficacy. To date, additional research is being conducted to further enhance ECT and TMS treatment, and to further define their role in treatment algorithms.

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Major depressive disorder (MDD) is a common and debilitating psychiatric illness that affects an estimated 121 million people worldwide [101]. According to the WHO, depression is among the leading cause of global disability worldwide [101]. Moreover, it is estimated that less than a quarter of those afflicted have access to effective treatments [101]. Severe depression can ultimately lead to suicide and, according to the WHO, leads to the loss of an estimated 850,000 lives each year [101]. Therefore, it is a high priority to develop safe, durable and decidedly effective forms of treatment for MDD. Antidepressant medications are the most commonly utilized initial form of treatment for MDD used in clinical practice. However, as illustrated by the STAR*D study, just over half of patients achieved remission following two adequate antidepressant medication trials [1–3]. Thus, while some patients do indeed benefit from pharmacotherapeutics, a considerable portion of patients do not experience significant relief of the depressive episode with the use of antidepressant medication alone [4]. This form of depression, commonly referred to as treatment-resistant depression (TRD), is the focus of many somatic neurostimulation modalities, including electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS). The purpose of this critical review is to synthesize available clinical information regarding the provision, efficacy and safety of ECT and repetitive TMS (rTMS), and to discuss their utility as antidepressant strategies for MDD and TRD.

Literature review methodology

To accomplish the literature review, independent searches were performed in the PsychInfo (1806–2012), Medline (1948–2012) and PubMed (1966–2012) databases with the following terms: 'electroconvulsive therapy' (including 'ECT', 'ECT therapy', 'electroshock therapy', 'EST' and 'shock therapy') and 'transcranial magnetic stimulation' (including 'TMS' and 'repetitive TMS'). To control for duplicate information and redundancy, the results of the independent database searches were imported into and managed with Endnote (version X5 for Windows, The Thomson Corp., CT, USA). A total of 62 articles that mentioned ECT or TMS (or one of the variants mentioned above) were included. These studies dated between 1985 and 2012, were written in the English language and were from national (USA) and international sites.

Electroconvulsive therapy

ECT continues to prevail as the oldest of the somatic therapies presently available for the treatment of many psychiatric disorders, most notably MDD [5,7]. Principal indications for ECT include severe depression with lack of response or intolerance to antidepressant medications, mania, psychosis, catatonia and acute suicidality, which requires a rapid rate of response [7–9]. A recent meta-analysis conducted by Dierckx *et al.* highlights the effectiveness of ECT in the treatment of bipolar disorder and suggests its effectiveness is comparable with that of unipolar depression [10]. In addition, ECT has historically been known to be effective in treating the melancholic depressive subtype, however, its use has been expanded more recently to include the atypical subtype of MDD [7]. Indeed, Mental Health America, formerly known as the National Mental Health Association, estimates that approximately 100,000 individuals undergo ECT each year [102].

Description of ECT

ECT is a highly effective technique used for the treatment of affective and psychotic psychiatric disorders that utilizes the induction of electrical currents within the brain to produce therapeutic tonic–clonic seizures [11]. The electrical current induces diffuse cortical activation, thereby producing robust therapeutic antidepressant effects. Ample research is underway to illustrate the mechanism of ECT. One hypothesis implicates the beneficial effects of ECT through its induced changes in cerebral metabolism, most notably within the limbic/paralimbic and neocortical structures [12]. Additional studies using functional MRI techniques suggest that the underlying mechanism of ECT may involve a decrease in functional connectivity within specific regions of the brain [13]. The 'hyperconnectivity hypothesis' of depression proposes that aberrant intracortical and corticolimbic connectivity networks are involved in eliciting affective disorder pathology. Moreover, hyperconnectivity in such regions may serve as a biomarker for mood disorders, in addition to a therapeutic target [13]. ECT appears to substantially impact one region of the brain that has historically been associated with depressive symptomatology and cognitive functioning, namely the left dorsolateral prefrontal cortex (DLPFC) [13].

Most ECT therapeutic protocols usually administer sessions two- to three-times per week

either on an inpatient or outpatient basis [8]. The number of treatments required to produce a therapeutic response can vary among individuals, however, the general range is from six to 12 treatments [8]. A recent systematic review conducted by Charlson *et al.* suggested that ECT administered twice-weekly resulted in an equivalent efficacy as ECT given three-times per week [14]. Although there is no general consensus among practitioners regarding the optimal frequency for ECT sessions, most would agree that fewer sessions would be desirable as this may result in fewer adverse effects [14].

■ Effectiveness of ECT

"Electroconvulsive therapy remains the most effective acute form of antidepressant treatment" [15]. The overall remission rate of ECT has been reported to range between 75 and 83% [16,17]. Although recent studies indicate that ECT has lasting effects on the functional architecture of the brain [13], most patients require additional antidepressant therapy upon completion of the acute ECT course to prevent relapse of depressive symptoms. For instance, without any continuation treatment, approximately 80% or more of patients will experience a relapse of depressive symptoms [18]. Utilization of antidepressant pharmacotherapy and/or continued ECT (commonly referred to as maintenance or continuation ECT) following an acute ECT course has shown to prolong remission in a significant proportion of patients [18–20]. Kellner *et al.* compared the effects of continuation ECT and pharmacotherapy in decreasing post-treatment relapse rates [19]. Both methods of continuation treatment were comparable and resulted in sustained remission rates of approximately 46% [19]. It has also been demonstrated that a combination of antidepressant and mood-stabilizing medications is an effective alternative pharmacologic maintenance intervention [21]. Currently, new strategies are being developed to prolong remission after a successful acute ECT course. For example, one such option includes the combination of ECT and pharmacotherapy during the acute and continuation treatment course.

■ Associated risks with ECT & methods to minimize risks

Contrary to some common opinions, ECT is safe and there are no absolute contraindications to its use as a psychiatric treatment [8]. However, with continued research and refinement, ECT is continually being optimized to enhance its efficacy and further improve its side-effect profile. The most notable and frequently encountered adverse effects associated with ECT regard those within the neurocognitive domain. These too have been minimized with the implementation of optimal ECT administration techniques [22]. Research has shown the extent of memory difficulty to be associated with specific treatment parameters, thus, current recommendations advise for the use of those parameters that help preserve cognitive abilities. For example, a combination of ultra-brief pulse width, right unilateral electrode placement and empirical dose titration may confer more cognitive advantages relative to other technical combinations [23]. As a result of utilizing such optimized treatment techniques, current evidence suggests that most neurocognitive complications are relatively limited in duration and may resolve within 2–4 weeks after the acute treatment course [24]. Continued research is warranted to better characterize the reported cognitive adverse effects, as well as to develop cognitive remediation paradigms to assist in preventing cognitive adverse effects [25].

Growing empirical evidence suggests that individual stimulus parameters influence effects on the clinical outcome and, as such, may be altered to reduce ECT-related risks [26]. For instance, cautious determination of pulse amplitude may effectively limit the amount of neural tissue being directly stimulated [26]. Mounting evidence also suggests that lower amplitude and/or pulse width coupled with increased dosage (number of pulses) successfully diminishes the frequency of adverse effects and improves overall treatment efficacy [26]. Perhaps future research will be better elucidated if enhanced specificity of stimulation can be achieved with the use of unidirectional pulse trains rather than the rectangular waveform with alternating polarity, commonly utilized in contemporary ECT [26]. Preliminary data from a recent study by Roepke *et al.* suggested that lower frequency (40 Hz) administration of suprathreshold right unilateral ultra-brief pulse ECT may be superior to higher frequency (100 Hz) stimulation [27].

Efforts to reduce ECT-related risks include the routine use of short-acting anesthetic agents and muscle relaxants and continuous medical monitoring. The implementation of such agents in routine clinical use has greatly improved the safety and tolerability of ECT [28]. Anesthesia has also been found to influence the efficacy of

ECT by significantly affecting the quality and duration of the induced seizure [29]. To obtain the therapeutic antidepressant effects of ECT, a well-generalized seizure of adequate duration (e.g., 15–20 s of motor seizure activity) is required [29]. Preferred anesthetic agents are those that have short half-lives, minimally influence seizure duration and ensure hemodynamic stability [30]. Commonly utilized anesthetic agents, such as methohexital, etomidate, propofol and thiopental, also have potent anticonvulsant properties. Methohexital is frequently preferred due to its minimal anticonvulsant effects and favorable cardiac side-effect profile [30]. Of the hypnotic agents, propofol can produce a considerably shortened seizure duration in addition to an increase in mean blood pressure [30]. Accordingly, the use of propofol may consequently hinder the effectiveness of ECT treatment despite resulting in an earlier return of cognitive function [30]. In a recent randomized, double-blind, controlled clinical trial comparing the effects of etomidate and sodium thiopental, Abdollahi *et al.* suggested that anesthetic induction using etomidate may be superior to thiopental in optimizing seizure duration, thus improving depressive symptoms [31]. Succinylcholine is a commonly used muscle relaxant owing to its rapid onset of action and short half-life [8]. In addition to anesthetic and muscle-relaxant agents, continuous medical monitoring, including blood pressure, ECG, EEG monitoring, pulse oximetry and measurement of end-tidal carbon dioxide, further optimize safety [8].

One potential alternative to ECT, which has demonstrated considerable promise, is magnetic seizure therapy (MST). The use of a magnetic field versus an electrical current to provide transcranial stimulation offers the distinct advantage of increased localization, which is necessary to reduce the cognitive side effects observed during ECT. The use of a more focal or localized form of neurostimulation means that the targeting and avoidance of specific cortical regions can be optimized to improve the antidepressant response of MST, while limiting or even eliminating the cognitive impairment following treatment. The increased precision and focal nature of MST is due to the lack of impedance experienced by a magnetic stimulus as it passes through the skull [32,33]. The advantage of inducing a therapeutic seizure with a more focal or localized form of neurostimulation has resulted in the continued development and investigational use of MST as a treatment for depression and as a potential alternative to ECT.

Transcranial magnetic stimulation

TMS is a neurotherapeutic technique first established by Barker *et al.* in 1985 [34]. Overall, an estimated 20–40% of patients are either intolerant to or do not adequately benefit from established antidepressant treatments, including pharmacotherapy, psychotherapy and ECT, thus, warranting the need for further neurotherapeutic innovations [4,35]. In October 2008, the US FDA approved the first rTMS device (NeuroStar TMS Therapy System™, Neuronetics, Inc., PA, USA) specifically for the "treatment of patients with medication refractory unipolar depression who have failed one good (but not more than one) pharmacological trial" [36]. To date, published meta-analyses support the statistical and clinical efficacy of TMS as a treatment for MDD [35,37–39]. Since its inception as a neurotherapeutic tool for depression in 1993 [40], the therapeutic utility of rTMS has extended to other psychiatric illnesses, including, but not limited to, hallucinations, bipolar disorders, acute mania, panic, obsessive–compulsive disorder, schizophrenia, post-traumatic stress disorder, catatonia and substance abuse [36,39].

Description of TMS

TMS utilizes ferromagnetic-stimulating coils that are capable of producing pulsating magnetic fields to noninvasively induce electrical currents within localized cortical regions [35,38,41]. The electric currents produced by TMS are of lower intensity than those used during ECT and, as a result, the antidepressant effects of TMS are achieved without seizure induction [41]. The ensuing electrical field is of sufficient force to focally depolarize neurons and, via the effects of long-term potentiation, can modulate cortical excitability with repetitive stimulation [26,36,41]. Such modulation is sustained beyond the time of stimulation and, in addition to producing localized effects, probably also generates indirect functional effects in cortical regions distant to the site of stimulation responsible for therapeutic results [35,42]. In addition, it has recently been suggested in preclinical research that the antidepressant effects achieved by rTMS may be associated with hippocampal neurogenesis [43].

TMS can be delivered in a variety of forms, including single-pulse TMS, theta burst and rTMS stimulation [36]. rTMS is the most

commonly utilized technique for the treatment of depression and is generally delivered at a high frequency (>10 Hz at 120% of the motor threshold) over the left DLPFC, otherwise known as fast left [44]. In addition, it has been suggested that low frequency stimulation (<1 Hz at 120% of the motor threshold) over the right DLPFC, referred to as slow right, also has significant therapeutic potential and warrants additional research [39,44,45]. Additional factors, such as coil positioning, frequency, pulse duration and stimulation intensity, are also implicated in the therapeutic efficacy of TMS. Results from a large-scale, federally funded clinical investigation demonstrated that stimulation at 120% of the motor threshold unadjusted for scalp–cortex distances is preferred for the treatment of MDD [46].

A typical course of rTMS consists approximately of 20–30 treatments delivered daily over the course of 3–6 weeks [47]. Each individual treatment can range between 40 and 60 min in length [47]. A recent study by Galletly *et al.* suggested that efficacy is dependent upon the number of treatments given, and that spacing the treatments over time neither improved nor diminished therapeutic benefit [48]. Aside from administering the typical 30 TMS sessions over 30 days, a new paradigm suggests there may be a benefit in administering 15 sessions in just a span of several days, which is referred to as accelerated rTMS [47]. Regular and accelerated rTMS have been found to have comparable safety and efficacy rates. To date, there is no consensus on the optimal number, frequency and spacing of rTMS treatments; however, continued research with TMS will help to provide answers to such important questions.

■ Effectiveness of TMS

rTMS is a commonly utilized therapeutic alternative for TRD [37]. Overall, much of the current available literature regarding the efficacy of rTMS is inconsistent, as the proposed rates vary considerably between studies [49–52]. For example, one of the largest multisite trials conducted to date demonstrated that remission rates were twice as high with active versus sham rTMS treatment [37]. The cause of this is likely to be multifactorial and includes methodologic differences, such as study-site selection across the globe (e.g., US vs Europe), enrolled patient population (e.g., different levels of medication resistance, sociodemographics and psychiatric disease) and selection of treatment parameters (e.g., high vs low frequency, different coil types and cortical site of stimulation). The number of prior antidepressant treatment failures has been recently established as one of the strongest predictors of favorable rTMS response [53]. Specifically, rTMS has been found to have greater efficacy in those patients who have failed only one antidepressant medication of adequate dose and duration. Consequently, rTMS is commonly utilized for the treatment of mild-to-moderate depression, and current practice guidelines includes the use of rTMS after one antidepressant medication failure of adequate dose and duration. Additional clinical and sociodemographic factors associated with a positive treatment outcome include shorter illness duration, absence of comorbid anxiety and female gender [53]. Owing to the excellent safety and tolerability of TMS treatment, further consideration of utilizing rTMS as a first-line treatment is warranted. In addition, recent research has suggested that rTMS may also be used as a form of continuation therapy, however, further evidence is needed to guide therapeutic paradigms [45,54]. Exactly where TMS fits into the depression treatment algorithm still remains to be determined. Additional research is currently underway with the hope of further enhancing the antidepressant potential of TMS therapy.

■ Associated risks with TMS & methods to minimize risks

One aspect of rTMS remains paramount – the excellent safety and tolerability of rTMS treatment [35,37,38]. The direct cortical stimulation achieved by rTMS is unique in that it does not result in widespread systemic effects, thereby lessening side effects and increasing tolerability. Although rTMS has been found to be relatively safe, it is possible that rTMS can induce hypomanic/manic symptoms and seizures [38,55]. However, the incidence of these adverse effects is exceedingly rare and can be avoided by carefully screening patients for known risk factors, in addition to strictly adhering to recommended rTMS stimulation parameters [38]. The most frequently reported adverse effect of rTMS involves localized irritation and/or discomfort during treatment at the site of stimulation. The occurrence of procedural pain may decrease tolerability of rTMS treatment [56]. Results from the open-label phase of a multisite trial demonstrated an overall decrease of 48%

in procedural pain by the third-treatment week [56]. This decrease in pain was probably due to an accommodation effect produced by repeated treatment and was unrelated to the antidepressant effect of rTMS [56]. Unendurable or persistent pain may be treated with over-the-counter analgesics, pretreatment topical lidocaine [57] or by changing the frequency of treatments. Although infrequent, other reported adverse effects include headache, insomnia and generalized somatic complaints (e.g., gastrointestinal disturbances). In addition, rTMS produces an audible clicking sound that may result in hearing loss with repeated treatments, making the routine use of ear plugs necessary [38]. Furthermore, TMS has not been shown to increase the risk of suicide as with other antidepressant therapies. Extensive research has demonstrated no known risk for cognitive impairment with TMS [58]. rTMS is a relatively novel therapy and as a result, the long-term effects of rTMS are unknown. To date, clinical research has demonstrated rTMS to be a safe and well-tolerated therapeutic option.

Discussion

Pharmacotherapeutic agents have predominantly been the first-line treatments for MDD. Although valuable, they are limited in their ability to effectively decrease depressive symptoms in the acute and continuation phases in a wide range of patient populations. Somatic therapies, including ECT and rTMS, are among several unique neurotherapeutic antidepressant strategies presently available (see **Table 1** for summary). While both of these treatments are placed as second-line therapies in the treatment algorithms, their safety and efficacy either match or exceed those of pharmacotherapeutics [16,17,37]. Indeed, ECT remains one of the most effective treatments for severe major depression [8,16,17,37], and rTMS continues to demonstrate good safety and efficacy rates, with continued enhancement with newer technical developments (e.g., new coil types) [35,37,38,59].

Whereas both ECT and rTMS are neurotherapies, they have considerable differences with regards to technical provision that limits direct comparison of their safety and efficacy. For example, ECT uses electrical stimuli to generate a tonic–clonic seizure in cortical tissue in order to produce therapeutic benefit [28]. Conversely, rTMS uses magnetic pulses to generate electrical activity in cortical tissue, without seizure propagation [60]. Thus, each has a distinct safety and efficacy profile and a unique role in the psychiatric armamentarium.

Table 1. Treatment provision information regarding electroconvulsive therapy and repetitive transcranial magnetic stimulation.

Domain	ECT	rTMS
Equipment	Thymatron (Somatics, Inc., IL, USA) Mecta (MECTA Corporation, OR, USA)	NeuroStar TMS Therapy System™ (PA, USA) Other rTMS stimulation devices are available, although are not US FDA approved
Treatment administrator accreditation requirements	Licensed physician Licensed anesthesiologist	Trained professional (licensed physicians, technicians, psychologists, physicists, physiotherapists and engineers)
Requires medical assistance	Yes	Recommended, but not required
Number of treatments	6–12	20–30
Average number of treatment weeks	2–4	3–6
Inpatient/outpatient	Both	Outpatient
Average inpatient hospitalization duration (weeks)	2–4	N/A
General anesthesia required	Yes	No
Continuation therapy available	Yes	Yes

ECT: Electroconvulsive therapy; N/A: Not applicable; rTMS: Repetitive transcranial magnetic stimulation.
Data taken from [8, 36, 45, 54].

Conclusion & future perspective

In conclusion, ECT and rTMS are effective and safe therapeutic options for the treatment of MDD. As ongoing research will further enhance the safety, efficacy and tolerability of these procedures, their use within treatment algorithms is likely to be expanded. For instance, the excellent safety and tolerability profile of rTMS may make it suitable as a first-line treatment option. However, additional research is needed in order to determine if rTMS would indeed be a judicious option before the initiation of other therapeutic regimens. Moreover, future research may determine if rTMS and ECT can be effectively employed as a combined form of therapy, where ECT is implemented as an acute treatment that is followed by the provision of rTMS during the continuation and maintenance phases. As new and innovative research ensues, neurostimulation modalities, including ECT and rTMS, will conceivably grow in prominence as valuable and useful treatments for psychiatric illnesses, specifically MDD.

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