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Geriatric Disorders (M Sajatovic and A Aftab, Section Editors)

The Efficacy and Safety of Neuromodulation Treatments in Late-Life Depression

Sanne J. H. van Rooij, PhD[1]
Patricio Riva-Posse, MD[1]
William M. McDonald, MD[1,2,*]

Address
[1]Department of Psychiatry and Behavioral Sciences, School of Medicine, Emory University, Atlanta, GA, USA
[*,2]Brain Health Center, Fuqua Center for Late-Life Depression, 12 Executive Park Drive, NE, Floor 5, Atlanta, GA, 30329, USA
Email: wmcdona@emory.edu

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Abstract

Purpose of Review In this review, the efficacy and safety of FDA-approved neuromodulation devices (electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulation (VNS)), as well as emerging neuromodulation treatments currently under investigation.

Recent Findings ECT is the "gold standard" somatic therapy for treatment-resistant depression (TRD). Although the clinical benefits are outweighed by potential cognitive and cardiovascular side effects in a majority of cases, it remains unfairly stigmatized. TMS has few cognitive or somatic side effects but is not as effective as the treatment of psychotic depression or more treatment-resistant depression in elders. VNS has limited data in older patients but has been shown to be effective in chronic, treatment-resistant adults. Several investigative neuromodulation treatments including magnetic seizure therapy (MST), focal electrically administered seizure therapy (FEAST), transcutaneous VNS (tVNS),

transcranial direct current stimulation (tDCS), and deep brain simulation (DBS) shown promise in geriatric TRD.
Summary ECT, TMS, and VNS are effective treatments for late-life depression, and research has continued to refine the techniques. Investigative neuromodulation techniques are promising, but evidence for the safety and efficacy of these devices in the geriatric population is needed.

Introduction

Approximately 7% of the US population over 60 years of age suffers from depression, and rates of treatment non-response to first-line pharmacotherapy and/or psychotherapy treatments are higher in older adults [1]. This heightened level of treatment non-response is possibly caused by age-related physiological changes that make geriatric patients more susceptible to antidepressant side effects and less likely to tolerate appropriate treatment dosage. Additionally, there is a higher likelihood of polypharmacy in older adults which increases risks for physical and cognitive impairments [2]. For many years, electroconvulsive therapy (ECT) has been the "gold standard" treatment for geriatric depression, but there is cumulative evidence for other neuromodulation treatments for late-life mood disorders. In this review, we will discuss the efficacy and safety of ECT and the other US Food and Drug Administration (FDA)-approved neuromodulation treatments for depression including transcranial magnetic stimulation (TMS) and vagus nerve stimulation (VNS). Emerging neuromodulation treatments in late-life depression will also be discussed.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is the most effective intervention for treatment-resistant depression (either unipolar or bipolar) across the life span [3]. As summarized in a meta-analysis by the UK ECT Review Group, six randomized controlled trials (RCTs) have demonstrated ECT to be more effective than sham ECT (effect size, 0.91), and 18 RCTs have shown it was more effective than antidepressant pharmacotherapy (effect size, 0.80) [4]. ECT is especially effective in older age with more rapid and higher remission rates, and lower rates of rehospitalization [5–7]. The reason for higher remission rates in older age is not clear, but is likely multifactorial including higher medication intolerance and earlier referral to ECT, as well as lower rates of comorbid personality disorders [8].

ECT is a generally safe and well-tolerated treatment including in elderly patients who may suffer from comorbid neurological, cardiac, and pulmonary disease [1]. The most serious adverse effects of ECT are cardiovascular complications. This is especially relevant to the elderly as they have higher levels of preexisting cardiac conditions including hypertension, coronary artery disease, and arrhythmias, which increases the potential for cardiac complications during ECT [9]. Yet, rates of cardiovascular side effects are low and concerns mainly apply to high-risk individuals which can be managed with prophylactic cardiac medications during ECT [3].

Another ECT side effect that is particularly important to consider in elderly patients is the potential for cognitive side effects. A relatively common side effect is a confusional state after ECT, lasting for about an hour after ECT, and likely the result of both the seizure and anesthesia. More severe, but less frequent, adverse effects include anterograde and retrograde amnesia which typically resolve in the first weeks after the completion of the ECT [8, 9]. When the cognitive side effects do appear during an acute course of ECT, these deficits typically recover within 6 months post-ECT [10•]. Brain disease and neuroanatomic changes (e.g., white matter hyperintensitities), decreased cognitive reserve, and simultaneous and administration of certain psychotropic medications (such as psychotropics with anticholinergic properties) are risk factors for prolonged or more severe cognitive impairments with ECT in the elderly [11, 12].

Several studies, including two NIMH trials, have demonstrated that the cognitive impairments resolve after ECT without long-term impact [7, 13–15]. Moreover, a meta-analysis (N = 2981) showed long-term cognitive improvements after ECT, likely as a result of the improvement in cognition related to the improvement in mood from ECT [16]. Furthermore, no evidence for irreversible neuroanatomic changes was found in autopsy studies on patients who received ECT with current techniques [17]. Additionally, structural magnetic resonance imaging studies demonstrate positive structural brain changes after ECT, including increased volume of the hippocampus [18•, 19•, 20], as well as increments in gray matter and fronto-limbic areas, and increased neurogenesis and neuroplasticity [21, 22].

However, there remains a small subset of patients with significant (subjective) retrograde amnesia that can extend to years before ECT [9, 23]. It is interesting that when patients were assessed for subjective memory impairment during their ECT course, more patients said their memory improved or remained unchanged during ECT, and only 16% of patients said their memory worsened during ECT [24]. In this study, 55% of patients reported after their course that ECT had an adverse effect on their memory perhaps due to negative expectations about a worsening of memory after ECT. More research is needed to better understand the risk factors for these subjective memory impairments.

The clinical effectiveness, as well as cognitive side effects of ECT, is influenced by (1) electrode placement, (2) magnitude of stimulus dose, and (3) electrical waveform. All these parameters are important in considering the risks and benefits of ECT in geriatric patients.

In clinical practice, three types of electrode placements are used: bitemporal (BT), right unilateral (RUL), and bifrontal (BF) ECT. While BT ECT has been demonstrated to have the highest effects [25], presumably because this electrode placement does not directly stimulate the language centers in the dominant hemisphere [26, 27]. However, the most comprehensive RCT to date compared all three electrode placements and showed no statistical differences in remission rates or cognitive side effects [13].

The second factor to consider in administering ECT in the geriatric population is the magnitude of the stimulus dose which is defined as the degree to which the stimulus dose is above the measured convulsive threshold for an individual patient and is directly correlated with the efficacy and cognitive side effects of ECT. Cognitive side effects increase when the stimulus is substantially

above the seizure threshold, and efficacy is directly related to the degree to which the stimulus is above the seizure threshold. This creates a risk/benefit ratio in which the seizure stimulus should be significantly above the seizure threshold in order to be efficacious but not so far above the threshold as to create unnecessary cognitive side effects without improving efficacy.

The efficacy of RUL ECT is correlated with an ECT stimulus substantially above the seizure threshold (i.e., at least 6 times over the seizure threshold) [28]. In contrast, BT ECT is effective at a stimulus dose that is 1.5–2.5 times the seizure threshold [29]. With age, the seizure threshold increases and therefore a higher stimulus intensity is required to elicit an effective seizure [30, 31] with the potential for increased cognitive side effects. Measuring the seizure threshold and using stimulus settings matched to an individual patient's convulsive threshold is a recommended form of personalized medicine with ECT, that can maximize efficacy and minimize cognitive side effects. In the RCT cited above (14), the efficacy of RUL ECT at 6× the seizure threshold was compared with BT and BF ECT at 1.5 times the seizure threshold and the efficacy and cognitive side effects of the three threshold placements was equivalent [13]. This study demonstrated the importance of measuring the individual seizure threshold to maximize efficacy and minimize cognitive side effects.

The third factor to consider is the electrical waveform. An important component of the electrical waveform is the pulse width which can be either a brief-pulse (BP) or ultrabrief (UB) pulse width. The pulse width can vary from 0.25–2.0 msec. BP is defined as 0.5 msec or longer, and UB is a pulse width of less than 0.5 msec. UB pulse widths have the advantage in being more efficient and can elicit seizures with less energy and have been shown to be associated with fewer cognitive side effects [32]. However, when using bilateral electrode placement, the use of BP is recommended as UB has been shown to be less effective [32].

The authors of a meta-analysis concluded that BP RUL ECT is more effective for depression and necessitates fewer sessions than UB RUL ECT, but was also associated with more cognitive side effects [33]. However, an RCT with four arms comparing BP or UB ECT and RUL (6× seizure threshold) or BT ECT (2.5 times the seizure threshold) concluded that UB RUL had the fewest cognitive side effects, and both BP and UB RUL ECT were equally effective and as effective as BP BT ECT [32]. UB RUL ECT may therefore have an advantage in elderly patients with depression.

The Prolonging Remission in Depressed Elderly (PRIDE) study [7, 34, 35••] was a multisite study evaluating the safety and efficacy of UB RUL ECT in 240 elderly adults (age > = 60) with MDD. Patients received RUL UB ECT with a frequency of three times a week. Results of phase 1 of the study showed that 61.7% of patients remitted (and 70% responded), 10% did not remit, and the other 28.3% dropped out. An average of 7.3 (SD = 3.1) sessions of ECT was needed for remission. Furthermore, although there were acute declines in some areas of neurocognitive performance (phonemic fluency, complex visual scanning, and cognitive flexibility), they were characterized as mild and most cognitive functions remained stable [35••]. UB RUL ECT was both well-tolerated and effective in treating geriatric depression. Overall, this study showed both the safety and efficacy of UB RUL ECT in the elderly.

The relapse rate in the 6 months following a successful course of ECT is estimated to be as high as 60% even when patients are maintained on

antidepressant medication [36–38]. Continuing ECT beyond the initial response has been shown to be successful in maintaining remission in depressed patients. The second phase of the PRIDE study demonstrated that as few as four additional continuation ECT treatments in the month following a successful course of ECT was more effective than simply discontinuing ECT in maintaining remission during a 6-month follow-up period [34].

In a prospective study, Kellner et al. confirmed the efficacy of continuation ECT over the 6 months following a successful course of ECT [39]. Other reviews, which have either focused on geriatric patients [40, 41] or included geriatric patients in their patient samples [42, 43], have supported the use of continuation and maintenance ECT.

Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) is an FDA-approved treatment for depression. TMS induces a magnetic field that creates an electrical field a few centimeters below the scalp and induces action potentials that stimulate cortical pathways critical in depression such as the dorsolateral prefrontal cortex. A meta-analysis pooling rTMS RCTs (N = 1371) showed a favorable response and remission rates for active (29.3% and 18.6% respectively) vs. sham rTMS (10.4% and 5%, respectively) [44].

Recently, the rTMS treatment parameters have expanded to include both high-frequency (up to 20 Hz) rTMS and low-frequency TMS (≤ 1 Hz) to the right or left dorsolateral prefrontal cortex (DLPFC) or bilateral stimulation, deep TMS (dTMS) which may stimulate areas of the brain deeper than the cortex and intermittent theta burst rTMS (iTBS) which applies a form of high-frequency rTMS that delivers brief trains of high-frequency pulses (50 Hz) that are repeated in 200 ms intervals (or 5 Hz which is in the EEG theta range (4–7 Hz) [45]. A recent meta-analysis of sham-controlled RCTs (N = 3058) demonstrated positive response rates for high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC; OR = 3.75), low-frequency over right DLPFC (OR = 7.44), bilateral rTMS (OR = 3.68), deep TMS (OR = 1.69), and iTBS (OR = 4.70) (37).

While over 30 RCTs have demonstrated the efficacy of rTMS over sham for depression, only 4 studies included geriatric patients (mean age > 60 years). Two of these studies targeted high-frequency rTMS over the left dorsolateral prefrontal cortex and showed a significant therapeutic effect [2]. Older and younger patients also showed similar response rates as demonstrated in an RCT (38) and a naturalistic study [46•].

rTMS has unique advantages over ECT for the treatment of late-life depression because it uses a subconvulsive and more focal electrical stimulation, which does not require anesthesia and is not associated with cognitive side effects. Some mild adverse effects include headaches, muscle twitches, and pain at the stimulation site and were no more common than with sham rTMS [47]. Seizures are the most serious adverse effect, though reports suggest a very low risk of 1 in 10,000 [41, 48].

Challenges with TMS response rates in the elderly are related to the TMS mechanism of action. Only cortical neurons within a few centimeters of the skull

are activated, and the magnetic field strength decreases with distance from the coil; efficacy can be impacted by age-related morphological and connectivity brain alterations [2, 49]. Vascular damage of the frontal-subcortical structures, hypothesized to be a contributor to some types of late-life depression, may reduce TMS efficacy in the elderly [50, 51]. In addition, cortical atrophy can increase the distance between the TMS coil and the cortex thereby reducing its efficacy. This was confirmed in two studies which showed a negative relationship between frontal cortex volume and a reduction in depression symptoms in elderly patients [52, 53].

White matter integrity, often compromised in elderly patients with risk factors for cardiovascular disease, is related to TMS-induced cortical excitability [54, 55] and motor learning changes [56]. This suggests that decreased white matter integrity could dampen TMS efficacy. Although smaller gray matter volumes have been associated with a decreased response to TMS, the presence of vascular disease can be mitigated by increasing the number of TMS pulses [53]. Importantly, the response and remission rates in geriatric patients are similar to younger adults when the stimulus intensity and number of pulses are increased [49, 57, 58]. Together, these studies support the use of rTMS for late-life depression if appropriate treatment parameters are used, and therefore merely underscore the importance of the development of protocols specifically for older patients.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is an FDA-approved treatment that requires surgery to place a bipolar electrode on the left vagal nerve connected to a stimulator in the chest wall. VNS is typically used as an adjunctive long-term treatment for chronic depression [59]. The pivotal open-label trial showed a response rate of 27% and a remission rate of 16% [60]. A five-year observational study conducted at 61 sites and including 795 patients showed that patients with treatment-resistant depression who received adjunctive VNS had better five-year outcomes than the treatment-as-usual group including patients who had previously received ECT [61]. A recent meta-analysis including 22 studies (2 RCTs, 16 single-arm, and 4 non-randomized comparative studies) supports VNS as an effective treatment for chronic depression [62].

A major barrier to the use of VNS in clinical practice has been lack of insurance coverage, in part due to the fact that the Centers of Medicare and Medicaid Services (CMS) reversed its original approval of coverage for the procedure, after it had been FDA-approved. A majority of the elderly population depends on Medicare for authorization of this procedure. However, in February 2019, CMS posted a Final Decision Memo that expanded Medicare coverage for VNS through a Coverage with Evidence Development (CED). (https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=292)

Treatments Under Investigation

Several neuromodulation treatments are currently under investigation including magnetic seizure therapy (MST), focal electrically administered seizure therapy (FEAST), transcutaneous VNS (tVNS), transcranial direct current stimulation (tDCS), and deep brain simulation (DBS).

MST is a convulsive therapy that induces a therapeutic seizure under anesthesia, but differs from ECT in that it uses TMS with a very high frequency (50–100 Hz) to induce a more focal seizure in less than 10% of the brain, mostly in the frontal cortex. Small RCTs and open-label case reports have suggested that anti-depressant effects of MST are similar to ECT, but with fewer cognitive side effects [63–67]. Therefore, this therapy is promising, especially in the elderly with increased risks for cognitive side effects from ECT. More studies assessing MST efficacy and side effects specifically in older age are needed.

FEAST is an electroconvulsive method to induce more focal seizures. FEAST employs electrical stimulation like ECT, but uses a monopolar pulse instead of a bipolar pulse, concentrating the electrical stimulus in a smaller area in the frontal lobe. Two preliminary studies on FEAST showed clinically significant reductions in depressive symptoms (35–55%) as well as shorter recovery times [68, 69] in adults with depression. Only one case study in an older depressed patient (72 years) has been published, and it was demonstrated that FEAST appropriately induced a seizure with increased metabolism in the right PFC, but not in the medial temporal structures (associated with memory), as is observed with ECT [70]. FEAST needs further investigation, but could be a potential alternative to ECT because it is more focal and likely to be associated with fewer cognitive side effects.

Transcutaneous VNS is non-invasive technique that applies an electrical stimulation to the cervical nerve. Neuroimaging research in depressed patients showed increased functional connectivity between the right amygdala and left dorsolateral prefrontal cortex as well as a reduction in depression ratings after 1 month of tVNS treatment [71]. A study in 51 healthy older adults (≥ 55 years) showed that tVNS improved autonomic function, and some of quality of life, mood, and sleep measures [72•].

Transcranial DCS is a non-invasive treatment for which an anode and cathode are positioned to provide stimulation to specific areas of the brain. The anode and cathode are connected to the direct current stimulator that applies a low constant current of 1–2 mA to either inhibit (by cathodal stimulation) or increase (by anodal stimulation) neuronal firing. Both open-label and randomized controlled trials, mostly targeting the left DLPFC, have shown small to moderate clinical benefit for depression [73, 74]. However, tDCS has not been shown to be more effective than standard first-line antidepressants and is less efficacious for treatment-resistant depression [75]. One case study of a 92-year-old patient with depression showed a positive treatment effect of tDCS [76]. Subsamples of elderly in larger studies showed treatment efficacy for the strongest current (2 mA) and longer treatment durations [77]. Important benefits of tDCS are the low risk for adverse events, low cost, and easy accessibility. In fact, no significant cognitive side effects have been reported; instead, a possible positive effect on cognition has been demonstrated in the elderly [77]. Because of its imperative benefits, especially relevant to older age, tDCS is considered a promising treatment for geriatric depression. Though, studies are needed to demonstrate efficacy and assess other potential side effects of tDCS

alone or in combination with other treatments.

Deep brain stimulation (DBS) is an invasive treatment in which electrodes are placed intracranially using stereotactic surgery to stimulate a targeted brain region continuously. DBS has been used as an intervention for treatment-resistant depression as part of research studies [78]. While small open-label studies show promising response rates, larger RCTs have failed to show clear distinction between active DBS and sham DBS for depression (72). Yet, there is reason for optimism through investigation into the most appropriate targets, preferably personalized, as well as patient selection [78, 79]. Patients in the DBS studies are on average 40–50 years old, and no studies have specifically assessed DBS in the elderly. Only two geriatric patients have been reported to respond to DBS for depression [77]. One issue concerning eligibility for DBS is that patients need to be healthy enough to undergo neurosurgery, which can be a problem in older adults, though DBS has been demonstrated to be safe in the the treatment of movement disorders in elderly patients with Parkinson's disease [80]. DBS could be promising for geriatric depression after it has been demonstrated to be effective for the general treatment-resistant depression population.

New developments of neuromodulation treatments as assessed in other disorders, such as anxiety and PTSD, could become a focus of investigation for late-life depression. For example, for rTMS theta burst stimulation has been used experimentally for PTSD and showed great promise [45, 81] and could be important in the reduction of treatment duration. This is especially relevant as TMS is not appropriate for patients with severe psychotic depression or suicidal ideation with clear intent primarily due to the 6-week course of treatment.

Conclusions

This review provides an update on neuromodulation treatments for the elderly. ECT remains the most effective treatment for late-life depression. Table 1 outlines the advantages and disadvantages for each procedure.

Research over the last 30 years has continued to refine ECT technique to limit side effects, most notably cognitive side effects, while maintaining therapeutic efficacy. Specifically, UB RUL ECT has been shown to have fewer side effects, and the pivotal PRIDE study has demonstrated this treatment is well-tolerated and effective for depression in the elderly.

TMS is also a very promising treatment for geriatric depression and does not require anesthesia and has not been associated with cognitive side effects. The number of TMS studies in elderly is limited, but suggests similar efficacy as adult depressed patients when appropriate treatment parameters are used. Therefore, optimizing TMS treatment settings and using new developments such as theta-burst stimulation may provide an alternative treatment for some geriatric patients.

The data on VNS is less clear and awaits further studies in the elderly.

Several treatments under investigation, (e.g., MST, FEAST, tVNS, and tDCS) show great promise for treatment of the elderly, due to a better side effect profile by becoming more focal (MST and FEAST) or subconvulsive (tDCS). Evidence for the safety and efficacy of these innovative treatments in the geriatric population is limited, and new studies are warranted.

Table 1. Neuromodulation treatments for major depression

Treatment	Primary advantages	Primary disadvantages	Comments
Food and Drug Administration–approved treatments			
Electroconvulsive therapy (ECT)	Excellent database in geriatric treatment-resistant depression (TRD), continuation, and maintenance treatment. ECT is the "gold standard" for the treatment of the most severely ill patients including patients with psychotic depression.	Potential for cognitive and cardiac side effects; significant costs to providing an appropriate medical setting for ECT; the social stigma related to the treatment	ECT techniques continue to evolve. For example, ultrabrief right unilateral ECT has been shown to limit the cognitive side effects of ECT while maintaining efficacy in depression.
Transcranial magnetic stimulation (TMS)	No discernable cognitive or cardiac side effects; good data in the elderly to maintain efficacy with specific treatment modifications (e.g., increasing the intensity and number of pulses)	6 weeks of daily treatments may present practical problems; Insurance coverage often limits modifications to the TMS protocol.	TMS technique will need to be refined (increased intensity and/or pulses) to be effective in the most treatment-resistant geriatric patients.
Vagus nerve stimulation (VNS)	Evidence that VNS is an effective long-term treatment for chronic depression with no apparent cognitive or cardiac side effects; evidence that VNS may be effective in patients who have failed a trial of ECT.	Surgical procedure and efficacy may take months to become apparent; insurance coverage is difficult to obtain; limited data in the elderly	Centers for Medicare and Medicaid Services (CMS) will cover VNS when provided under the CMS-approved Coverage Evidenced Development plan.
Investigational treatments			
Magnetic seizure therapy (MST)	More focal stimulation than ECT that may provide the efficacy of ECT with fewer cognitive side effects	Involves anesthesia and the medical setting for ECT; limited data particularly in the elderly	More focal brain stimulation may provide a therapeutic effect without significant cognitive side effects
Focal electrically administered seizure therapy (FEAST)	More focal stimulation and the potential to decrease cognitive side effects with similar efficacy to ECT	Involves anesthesia and medical setting for ECT; limited data in the elderly	This is a similar approach to MST
Transcutaneous vagal nerve stimulation (tVNS)	Non-invasive form of VNS which has been shown to be safe and well-tolerated	Limited data in the elderly and TRD	This approach may have the advantages of VNS with a less-invasive procedure
Transcranial direct current stimulation (tDCS)	Preliminary data supports tDCS in the treatment of depression; safe, low cost, and easy accessibility	Limited data in the elderly and TRD	Has a number of potential advantages for the elderly if shown to be effective
Deep brain stimulation (DBS)	Published data shows that TRD patients, even patients who have not responded to ECT, respond to DBS.	Invasive surgical procedure; may take months to show response.	Data in Parkinson's disease may be useful in determining safety in geriatric TRD patients

Compliance with Ethical Standards

Conflict of Interest

Dr. van Rooij reports research support by the Brain and Behavior Research Foundation (NARSAD Young Investigator Award). Dr. Riva-Posse has received honoraria from Janssen Pharmaceuticals for serving in a

consulting board. Dr. McDonald reports research supported by the National Institute of Neurological Disease and Stroke, National Institute of Aging, Stanley Foundation, Soterix, Neuronetics, NeoSync, and Cervel Neurotherapeutics. He has a contract with Oxford University Press to co-edit a book on the Clinical Guide to Transcranial Magnetic Stimulation in the Treatment of Depression and section editor for Current Psychiatry Reports. He is a consultant for Signant Health. He also receives support from the JB Fuqua Foundation.

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