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# Brain stimulation in the treatment of late-life severe mental illness other than unipolar non-psychotic depression

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## Abstract

Late-life mental illness is a growing concern. Current medications have limited efficacy and are associated with safety concerns. A variety of brain stimulation approaches offer alternative treatments. We performed a systematic literature search on the efficacy and safety of brain stimulation in late-life mental illnesses, excluding unipolar non-psychotic depression. Studies on deep brain stimulation (DBS), electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and vagal nerve stimulation (VNS) that enrolled exclusively older adults (age 65 or older) or analyzed older adults as a separate group were included. The search identified 1,181 publications, of which 43 met the above inclusion criteria: 24 were related to the treatment of non-unipolar depression (ECT: 21; rTMS: 2; ECT and rTMS: 1), 14 to dementia (ECT: 7; VNS: 2; rTMS: 4; DBS: 1) – three ECT studies included under both depression and dementia – and 7 to schizophrenia (ECT: 7). These studies reported a high degree of variability in efficacy and safety with promising results in general, particularly in the treatment of dementia and schizophrenia. Most publications were limited by small sample sizes, lack of control conditions, and lack of randomization. Large studies with a randomized controlled design or other designs such as crossover or off-on-off-on are needed. In contrast to the empiric and nonspecific use of ECT, future studies using modalities other than ECT could focus on novel biologically-based interventions that can target specific circuitry. These interventions could also be combined with other non-brain stimulation treatments for possible synergistic effects.

### Keywords

brain stimulation; elderly; ECT; mental illness; transcranial magnetic stimulation



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## OBJECTIVE

With the worldwide aging of the population, the numbers of older adults with other severe mental illnesses is increasing. For example, the number of individuals with schizophrenia will double (2) and those with Alzheimer's disease (AD) will quadruple over the next few decades (7). Efficacy of psychiatric medications in the treatment of late-life mental illnesses is affected by age-related pharmacokinetic changes, increased probability of drug-drug interactions, pharmacodynamic changes (e.g., increased sensitivity to adverse effects), and difficulties with adherence (3). Safety of psychiatric medications is also a concern in late life. For example, anticonvulsants are associated with an increased risk of suicidal acts or violent deaths (4, 5); antidepressants are associated with an increased risk of falls (6) or bleeding (10); and antipsychotics are associated with an increased risk of mortality (7–9).

Given the limitations of psychotropic medications, alternative treatments are needed. Brain stimulation approaches offer a viable alternative for some older patients, especially those who do not respond to or tolerate medications (11). This paper systematically reviews current evidence relevant to the use of brain stimulation interventions in older adults for the treatment of severe mental illness. However, we exclude unipolar non-psychotic depression because the literature on the use of brain stimulation in its treatment is immense and necessitates a separate review.

## METHODS

### Search strategy

EMBASE, Ovid Medline, and PsycINFO were searched on March 7, 2012. No date limits were applied. The following search terms were used: ((electroconvulsive therapy) OR (transcranial magnetic stimulation) OR (transcranial direct current simulation) OR (vagus nerve stimulation) OR (deep brain stimulation) OR (rTMS) OR (magnetic seizure therapy)) AND ((psychosis) OR (anxiety) OR (dementia) OR (addiction) OR (mental* ill*) OR (schizophrenia) OR (cognition) OR (bipolar)). To focus on studies with older adults, the search was limited to "all aged (65 and over)" OR "aged (80 and over)." Other limitations used were "human", "English", and "peer-reviewed journal."

### Inclusion and exclusion criteria

We included studies that either enrolled only older adults or analyzed older adults as a separate sample. We excluded publications that did not use brain stimulation, used brain stimulation only as an investigational rather than a treatment tool, or reported only on unipolar depression or on a neurological disorder without a co-morbid psychiatric illness. Investigational use was defined as the use of brain stimulation to assess the function of a brain region or circuit, typically by applying the brain stimulation once to that region. In contrast, therapeutic use is defined as the use of brain stimulation to assess its effect on a clinical outcome, typically through a repetitive course.

### Classification and description of studies

If a publication met the above eligibility criteria, we classified it based on the psychiatric illness that was treated with brain stimulation. After selection and classification, we recorded the journal name, title, first author, and year of publication. Other information recorded included the aim, sample size, participants' age and gender, brain stimulation protocol, and major findings. Then, we summarized information about efficacy, safety, and predictors of response when available.

## RESULTS

The search identified 1,181 publications. 1,137 were excluded and 43 publications were retained: 24 were classified under non-unipolar depression (ECT: 21; rTMS: 2; ECT and rTMS: 1); 14 under dementia (ECT: 7; VNS: 2; rTMS: 4; DBS: 1) – three ECT studies included under both depression and dementia – and 7 under schizophrenia (ECT: 7). No publications retrieved reported on the use of brain stimulation in the treatment of addiction or anxiety, or on the use of transcranial direct current stimulation or magnetic seizure therapy (MST).

### Non-Unipolar Depression

Twenty-four publications (see Table 1) reported on the use of brain stimulation in the treatment of non-unipolar depression in older adults. Participants were diagnosed with bipolar depression (2 publications), depression and dementia (8 publications), psychotic depression (12 publications), vascular depression (1 publication), and mixed (1 publication).

**Bipolar depression—**One retrospective review of 56 adults, mean age of 48 (SD = 15), with bipolar depression described the clinical and demographic predictors of remission in response to rTMS treatment. Patients had a mean of 3.5 depressive episodes (SD = 1.5). They all achieved remission after a median of 15 rTMS sessions (interquartile range, 10–20). While the majority of the patients received 20 Hz rTMS over the left dorsolateral prefrontal cortex, six received 1Hz rTMS over the right dorsolateral prefrontal cortex. Also, six received rTMS at less than 100% of the motor threshold. All patients received rTMS until remission, defined as Hamilton Depression Rating Scale (HDRS) (12) scores < 7. Older age, refractoriness as defined by two or more failed antidepressant/mood stabilizers trials, number of prior depressive episodes, and severe depression at baseline were associated with more than 15 sessions to achieve remission (13). However, in a multivariate analysis, only refractoriness and severity of depression remained significant. Common adverse effects were somnolence (n=2), headache (n=6), and nightmares (n=3). Hypomania was also seen in four patients (13). This study suggests that older patients with bipolar depression show a similar pattern of response as younger patients with comparable illness severity when treated with high frequency rTMS and at 100% motor threshold intensity. These findings need to be confirmed in randomized controlled trials. Given that with older age the distance between scalp and brain tissue increases, other variables could also be assessed such as whether supratheshold intensity would result in higher rates of remission and less number of sessions to achieve remission; and whether deep rTMS is more efficacious and efficient than rTMS.

One case series involving two patients with bipolar depression and long bone fractures described significant improvement with ECT treatment without musculoskeletal complications (14).

### Depression with dementia

**ECT and rTMS:** One retrospective chart-review study assessed the use of ECT and rTMS in treating depression among 14 hospitalized patients with dementia with Lewy Bodies (DLB), age 50 or above. Eight patients received bifrontotemporal ECT (0.5 ms pulse) and experienced a significant reduction on HDRS scores from a mean of 38.0 (SD = 5.8) before ECT to a mean of 15.0 (SD = 9.6) after ECT ($p < 0.005$). Six patients received rTMS daily for 10 days according to the following protocol: a train of 140 pulses at 1 Hz delivered to the right dorsolateral prefrontal cortex at 110% motor threshold and repeated 3 times per day with a 30-second inter-train interval, followed by a train of 50 pulses at 10 Hz delivered to the left dorsolateral prefrontal cortex at 100% motor threshold and repeated 15 times per day

with a 25-second inter-train interval. Patients experienced a significant reduction in HDRS scores from a mean of 24.0 (SD = 8.0) before rTMS to a mean of 11.0 (SD = 5.9) after rTMS ($p < 0.005$) (15). It was noted that that patients who received ECT had a treatment-resistant depression as defined by failing at least two antidepressants trials. This was not the case for those who received rTMS. This study reported no side effects from either intervention.

The improvement observed following ECT in the above study is consistent with a case series describing seven patients with depression and suspected DLB, all of whom responded acutely to bitemporal ECT. This case series also described a stabilizing effect among three out of the four patients who received continuation-maintenance ECT. Other than prominent post-ECT confusion, there was no change in cognition. No significant impact was also noted on the motor or parkinsonsian features of DLB (16). Another retrospective chart-review study compared ECT outcomes between older patients, age 60 or above, hospitalized with a diagnosis of major depression with dementia (n=21) and those with major depression alone (n=84) (17). Patients received non-dominant unilateral ECT. Using a simple 4-point scale (0 = no improvement or worse, 1 = mild improvement, 2 = moderate improvement, and 3 = marked improvement), there was no difference in the extent of improvement between the two groups. However, female patients with dementia and depression had poorer outcomes than female patients with depression alone (mean improvement rated 1.6 versus 2.3, $p = 0.007$). There was no difference between the two groups of male patients (17). Also on a 4-point scale (0 = less than 1 hour, 1 = less than 24 hours, 2 = 1–2 days, and 3 = more than 2 days), patients with dementia and depression experienced more prolonged confusion than those without dementia (mean duration of confusion rated 1.0 versus 0.35, $p = 0.02$). Otherwise, there was no difference in tolerability including cardiac complications (17).

A third retrospective chart-review study assessed the impact of ECT on mood and cognition among 31 hospitalized patients with dementia (55% vascular, 13% AD, and 32% uncertain) (18). They ranged in age between 55 and 97 (mean 75.6, SD = 9.9) and 81% were female. Out of the 31 patients, 22 received unilateral and nine received bilateral ECT. Patients received between 1 and 23 sessions (mean = 9, SD = 5.7) indicating a high degree of inter-individual variability in response times. On average, these patients experienced a significant mean decline on the Montgomery-Asperg Depression Rating Scale (MADRS) (19) of 12.3 points ($p < 0.01$). In addition, they experienced a significant increase on the Mini-Mental State Examination (MMSE) (41) of 1.6 points ($p < 0.02$) from a mean admission score of 18.8 (SD = 5.5). However, 15 out of the 31 patients experienced delirium between 1 and 3 days during the course of ECT. Other adverse events included one transient ischemic attack, one prolonged seizure, one atrial fibrillation, and one episode of ventricular tachycardia (18). This publication did not report an analysis comparing the unilateral versus bilateral ECT groups separately.

The findings of a prospective naturalistic study evaluating ECT among 40 hospitalized patients with various depressive disorders, age 60 or above are also consistent with the above findings (26). Among the 40 patients, 22 suffered from major depression with dementia and received unilateral ECT. Compared to these 22 patients, eight patients with major depression and dementia (with all except one treated with unilateral ECT) experienced comparable improvement in depression. Cognitively, most patients, especially those with dementia, experienced a significant increase in MMSE, from a mean of 16.3 (SD = 3.9) to a mean of 19.5 SD = 7.0) ($p = 0.04$). In this study, 13 out of the 40 patients experienced confusion between ECT sessions, including four patients with dementia; MMSE scores did not predict confusion (26).

Another prospective naturalistic study assessed the effect of ECT in the treatment of major depression among 44 hospitalized patients age 65 or above (mean age = 73, SD = 6) with AD (N = 12), Mild Cognitive Impairment (MCI; N = 19), or no cognitive impairment (NCI) (N = 13) (20). ECT was found to be efficacious in treating the symptoms of depression in all three groups. Cognition assessed by MMSE, also improved in patients with MCI and NCI six months post-ECT and did not change significantly in patients with AD. Only a minority of patients from any group experienced decline in MMSE at six months although most patients with AD experienced a decline after six sessions of ECT, and most patients with MCI experienced a decline at six weeks post-ECT. Baseline cognition but not mood symptoms predicted cognitive decline. Patients in this study received either unilateral (N = 32, 72.7%) or bilateral ECT. The study did not compare the cognitive effects between the two modalities.

These publications on ECT are consistent with three single case reports reporting on the beneficial effect of ECT in the treatment of depression with comorbid early-onset AD (21), advanced dementia (22), and frontotemporal dementia (23).

In summary, patients suffering from depression in the context of dementia seem to experience relief from depression in response to ECT. However, some of them experience prominent confusion and delirium especially with bitemporal ECT. It is less clear whether patients would experience similar benefits or adverse effects in response to other seizure-inducing modalities such as focal, unilateral, ultrabrief, or bifrontal ECT, or MST.

**Psychotic depression—**A number of publications have reported on the effect of ECT in older adults with psychotic depression. One prospective study assessed the effect of acute ECT on 30 hospitalized older adults with psychotic or non-psychotic depression, age 65 or above (mean age = 74.0, range = 65–88). The numbers of those with psychotic depression and those without were not reported. However, a graph suggests that about 10 out of 30 participants had delusions. After a mean of 7.1 session (range 4–14), participants experienced a reduction in mean MADRS (19) scores from 33.8 (8.7) to 11.7 (10.1) ($p < 0.0001$). Fifty percent of participants experienced a reduction of at least 80% from baseline, and 23% of participants experienced a reduction of 50–79% from baseline. The presence of delusions did not predict response. This study did not report any side effects (24).

Another prospective open-label and non-randomized study evaluated unilateral followed by bilateral ECT versus nortriptyline and perphenazine among 25 hospitalized patients with unipolar psychotic depression, age 60 or above. Seventeen participants received ECT and eight received pharmacotherapy. Response was defined by an HDRS score of 10 or less and the absence of delusions or hallucinations. Within the first 6 weeks of treatment, 15 (88.2%) participants responded to ECT while only two (25%) responded to pharmacotherapy ($p = 0.004$). Over a period of 8 weeks, participants treated with ECT responded on average three weeks earlier than those treated with pharmacotherapy. The paper did not report on side effects. In addition to the limitation of the design and the small sample size, the pharmacotherapy group was made up of participants who declined ECT (25).

In a prospective naturalistic study among 40 hospitalized patients age 60 or above, ten patients who were diagnosed with psychotic depression experienced higher reduction in their HDRS scocre (mean reduction: 78%, SD: 15%) in response to ECT than 15 patients with non-psychotic depression (mean reduction: 60%, SD: 23%) ($p = 0.04$) (26).

One randomized single-blind study of 33 adults with psychotic depression, age 60 or above, compared the efficacies of continuation/maintenance bifrontotemporal ECT plus nortriptyline (n=16) and nortriptyline alone (n=17) in preventing recurrence or relapse

following acute remission with ECT, that was typically achieved after 11 ECT sessions. Continuation/maintenance ECT was delivered as once a week for one month, then every two weeks for another month, then once a month. After two years of follow-up, four of the 16 participants who were maintained on ECT plus nortriptyline exited the study prematurely and one (6%) relapsed. In contrast, four of the 17 participants who were maintained on nortriptyline alone exited the study prematurely and eight (47%) relapsed or experienced a recurrence. The mean survival time to relapse or recurrence was significantly longer in the ECT plus nortriptyline group (23 months) than in the nortriptyline alone group (16 months). Overall both treatments were well tolerated and they did not differ with respect cardiovascular, cognitive, or other adverse effects. However, cognition was only assessed by the MMSE (27).

One case series described three older adults who were treated with ECT for depression – two of them with psychotic depression – while they received anticoagulation therapy for cardiovascular disease. All participants showed improvement in depressive symptoms with no significant adverse effects (28).

The above studies are consistent with eight single-case reports that reported on the beneficial effects of ECT in older adults with psychotic depression (29–36).

**Vascular depression—**One randomized double-blind prospective study assessed the efficacy rTMS in the acute treatment of 92 older patients with vascular depression. Patients were recruited from both inpatient and outpatient settings. They were defined as suffering from vascular depression on the basis of an age at onset of a first major depressive episode at age 50 or older and having at least three cardiovascular risk factors. The study consisted to two experiments. In experiment 1, participants received either sham or active rTMS treatment with the following characteristics: 10 rTMS sessions to the left dorsolateral prefrontal cortex and over a 10-day period, at a frequency of 10 Hz, intensity of 110% of the motor threshold, with 20 six-second trains per session, for a total cumulative dose of 12,000 pulses. In experiment 2, participants received either sham or 15 rTMS sessions (same characteristics as in experiment 1) with 2 sessions per day on 5 of the 10 days, resulting in a total cumulative dose of 18,000 pulses. Only the 18,000 pulses groups achieved significantly higher response (39.4%) and remission (27.2%) rates than the corresponding sham group (6.9% and 3.5%). There was a negative correlation between response and age. Common adverse effects were headache and local discomfort (37). Both active groups experienced improvement on one measure of executive function, independent of response. These findings raise a number of questions that will need to be clarified by future studies. First, should the number of pulses increase with age? If the number of pulses is critical in producing response or remission, would a TMS intervention that could deliver a large number of pulses in short periods of time such as theta-burst stimulation (38) be a preferred option? Finally, could rTMS be used to enhance cognition in patients with vascular depression or late-life depression in general. Given that cognitive deficits are associated with lack of response in late-life depression (39, 40), adjunctive rTMS could not only enhance cognition but also improve response to the pharmacologic or psychosocial interventions.

## Dementia

Fourteen publications (see Table 2) described the use of brain stimulation in patients with AD of varying severity (7 publications), vascular dementia (1 publication), mixed dementias (3 publications), unspecified dementia (2 publications), and MCI (1 publication).

**ECT—**We did not find ECT studies that assessed the effect of ECT on cognition in patients with dementia or MCI as a primary objective. Three ECT studies assessed the effect on

cognition in context of treating depression among patients with dementia studies. These are described under "***Depression with dementia***" above (18, 26, 20).

In addition, one case series reported on four hospitalized patients age 56 to 78 with dementia and severe behavioural and psychological symptoms including verbal and physical agitation and aggression that did not respond to psychotropic medications. After 2 to 4 ECT sessions, these four patients experienced a clinically meaningful reduction in their symptoms that lasted for 3 to 12 months despite the absence of maintenance treatment. Two patients relapsed and responded to a second short course of ECT. The effect of ECT on cognition was not reported (42).

Another case series reported on the effect of ECT on "mania" and agitation in three older patients with dementia. These three patients experienced clinically significant improvement in symptoms mania and agitation, as well as in cognition after a short course of ECT followed by maintenance treatments every two weeks (43).

The effect of a short course of ECT was also reported on in a 92 year-old female with vascular dementia and psychotic symptoms that failed to respond to haloperidol. After two sessions of bilateral ECT, the patient's behavioral and psychotic symptoms resolved with no clinical evidence of cardiovascular or cognitive deterioration. This response persisted during a three-month follow-up, with the use of an antipsychotic for the first month (44).

These results are consistent with a more recent retrospective chart review describing the use of ECT to treat agitation and aggression in 16 hospitalized patients (mean age = 66.6, SD = 8.3) with mild to severe dementia. In this study, 12 patients received only bilateral ECT as they were started on it, three patients received right unilateral ECT followed by bilateral ECT because of lack of response, and one patient received only right unilateral ECT. On average, patients received 9 treatments (range: 2 to 15) and experienced a clinically significant decrease in agitation, with all patients improving except for one (45).

In summary, ECT, particularly bilateral ECT, seems to be effective in the treatment of behavioral and psychological symptoms associated with dementia. The concern of worsening cognitive impairment is not substantiated by the current literature, notwithstanding the limitations of this literature. However, given the potentially serious adverse effects associated with psychotropic medications in this population, larger studies of ECT or other convulsive modalities thought to spare cognition (e.g., MST) are warranted.

**rTMS—**Four published rTMS studies from one research group have assessed the effect of rTMS on cognition in patients with AD. One prospective study assessed the effect of a combination of high frequency rTMS and cognitive training in patients with AD on cognitive function (46). Participants with a mean age of 75.4 (SD = 4.4) had mild to moderate AD and were ambulatory. The rTMS protocol consisted of delivering daily rTMS for 6 weeks and then twice a week for 3 months to six brain regions (three per day alternating with the other three): Broca's, Wernicke's, bilateral dorsolateral prefrontal, and bilateral parietal. Each region received 20 × 2-sec trains of 10 Hz rTMS for a daily total of 400 pulses per region or 1,200 pulses per participant over three regions. Cognitive training consisted of cognitive tasks that activate these regions and was delivered on the days that participants received rTMS. Assessments were performed at baseline, 6 weeks, and 4.5 months after rTMS and cognitive training were initiated. On average, participants' scores on the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog; 50) was 4.0 points at the 6-week and 4.5-month follow-up than at baseline. No improvement was noted on the MMSE (46). Although this positive result is encouraging, the relatively small

observed cognitive improvement is disappointing given the total cumulative dose that these participants received during the acute treatment (36,000 pulses).

Three controlled studies by the same group reported on the effect of rTMS on cognition in patients with AD (47–49). In one study, 15 ambulatory participants in their mid-70's, ambulatory with mild or moderate AD were randomized to receive three experimental blocks of left and right dorsolateral prefrontal cortex rTMS, and sham rTMS. Each block consisted of 600 milliseconds of rTMS at 20 Hz delivered before the cognitive assessment. Both left and right-sided rTMS resulted in improved action but not object naming compared to sham rTMS (47). A follow-up study included 24 participants with moderate or severe AD (MMSE 0–16) and found that, unlike participants mild or moderate AD (MMSE 17–30), those with moderate-severe AD improved on both action and object naming (48). The third study involved a 4-week course of 20-Hz daily rTMS or a 2-week course of sham rTMS followed by 2-week course of 20-Hz daily rTMS. Thus, participants received 20,000 pulses during each 2-week of active rTMS resulting in statistically significant improvement in auditory sentence comprehension that persisted for 8 weeks after the end of rTMS course (49). While the large observed effect sizes are encouraging, it is not clear whether the results would remain statistically significant after correction for the multiple comparisons that were performed.

In summary, rTMS appears to be a promising treatment for AD but this approach still needs further studies. In particular, several variables need to be elucidated including the number of pulses, frequency, site of stimulation, course duration, and concurrent use of other interventions such as cognitive training or cognitive enhancement. In addition, other TMS-based modalities are worth investigating. If rTMS is thought to enhance neuroplasticity via high-frequency stimulation, other TMS modalities (e.g., paired associative stimulation and theta-burst stimulation) that have also been described to enhance neuroplasticity in vitro should be investigated.

**VNS—**Two related studies assessed the effect of VNS on cognition in patients with AD. In one study, ten participants (mean age = 67.0, SD = 6.7) with mild to moderate AD were treated in a single blind trial and assessed three and six months following the implantation. Defining response as no change or improvement on the ADAS-Cog or MMSE, the study reported that seven participants were responders at three and at six months on ADAS-Cog, vs. nine and seven on MMSE. Following the implantation, participants were allowed to recover from the surgery for two weeks before VNS was turned on. When participants were assessed during these two weeks, i.e,. while VNS was still off, several participants met criteria for response compared to baseline, leaving only five participants with further response on ADAS-Cog between recovery and three and six months. In contrast, all ten participants experienced response between recovery and three months on MMSE, and seven at six months. However, only four participants experienced response between recovery and three and six months on both ADAS-Cog and MMSE (51, 52). A one-year follow-up study included seven more participants for a total of 17 participants followed for one year (51). At one year, 7 (41.2%) and 12 (70.6%) participants were classified as responders based on the ADAS-Cog and MMSE respectively. However, response was due to lack of cognitive deterioration rather than improvement and the median changes in ADAS-Cog and MMSE one year after baseline were not statistically significant. While VNS was generally well tolerated, changes in voice or hoarseness occurred in 16 of the 17 participants. Overall, it is not clear whether these findings are due VNS, implantation surgery, or a placebo effect. Control conditions would be needed to address this question. Given that hoarseness is a common side effect of VNS, blinding would be difficult. Other side effects in patients with AD have included hematoma at the site of implantation, inflammation, fainting post-surgery, cough, pain, and dysphagia (51, 52).

**DBS—**DBS of the fornix/hypothalamus was investigated in a phase I trial in six participants with probable AD who were on stable doses of acetyl cholinesterase inhibitors for a minimum of six months (53). Overall DBS was well tolerated: some participants experienced flushing, sweating, warmth, and increases in heart rate, and blood pressure. After six months of stimulation, four of the six participants experienced improvement on ADAS-Cog. However, after 12 months, only one continued to experience some improvement compared to baseline while the others experienced worsening. On the MMSE, two participants experienced improvement from one month to one year following the surgery while the others experienced no change or worsening. However, compared to an average decline of 2.8 points on the MMSE during the 11 months prior to the surgery, participants experienced an average decline of 0.8 points during the 11 months following the surgery. On FDG PET scans, DBS was found to reverse impaired glucose metabolism in the temporal and parietal lobes after 12 months of stimulation (53). There was also some improvement in glucose metabolism in frontal regions of the brain between one and 12 months; however, it continued to be decreased in these regions compared to baseline. These findings are promising and warrant a larger longer controlled study.

## Schizophrenia

Seven publications described the use of ECT in the treatment of schizophrenia and related psychotic disorders (54–60) in six prospective studies and one case series (56). Participants were between 49 and 96 years old. Two publications (54, 55) focusing on late-age onset psychosis (LAOP; defined onset after the age of 60) included participants over 65 years of age. Four studies (57–60) involved middle-aged (49–64 years old) and older participants with catatonic schizophrenia. No other brain stimulation modality has been studied in an exclusive sample of older patients with schizophrenia (see Table 3).

Bilateral ECT was found to be effective in treating chronic schizophrenia in a case series of five female patients aged 55 to 74 (56). All patients experienced a reduction of their psychotic symptoms with acute ECT. With maintenance ECT with or without antipsychotic medications, these patients experienced a remarkable increase in functional level. However, they were not assessed for any change in cognition.

Four prospective case series have evaluated the efficacy of bilateral ECT in treating middle-age and elderly patients with treatment-resistant catatonic schizophrenia (57–60). In a first study, ECT (12 sessions administered over 4 weeks) was found to be efficacious acutely in 9 of 9 patients as measured by the Brief Psychiatric Rating Scale (61), Global Assessment of Functioning Scale (GAF) (62), and Guy’s five factors (63) (thought disturbance, activation, anxiety-depression, hostility-suspiciousness, and anergia) (57). In another study, when eleven older patients who had responded to ECT were switched to maintenance antipsychotics, seven (63.6%) relapsed within 6 months. In a third study, 12 patients who relapsed after acute ECT treatment despite the use of maintenance antipsychotics were successfully treated with a second acute course of ECT. They were then switched to maintenance ECT (4 sessions once a week, then 4 sessions once every two weeks, and then 3 sessions once every four weeks) combined with antipsychotics (59). The relapse rate with continuation ECT plus antipsychotics was 25% (3 out of 12) (59). Then, those patients who relapsed on maintenance ECT plus antipsychotics were treated acutely for a third time with ECT and then switched to a more frequent schedule of maintenance ECT (8 sessions administered once a week, and then tapered on a case-by-case basis) combined with antipsychotics (60). One patients who relapsed 237 days after the third acute course was then treated with a fourth course of acute ECT, followed by more frequent maintenance ECT combined with an antipsychotic. He was maintained on this regimen for 1 year and 7 months, and was still in remission at the time of publication. A second patient was

maintained on ECT plus an antipsychotic for one year, and stayed in remission for almost 4 years after the completion of maintenance ECT. The third patient received 2 years and 3 months of maintenance ECT plus an antipsychotic and relapsed 7 months after the completion of maintenance ECT (60). Overall, ECT appeared to be well-tolerated in these studies. Post-ECT delirium was reported in three out of nine patients; however, it resolved within 3 days in all cases. One patient experienced supraventricular premature contractions during an ECT-induced seizure (57) No other severe adverse effects were reported (57–60).

In contrast to these cases of patients with catatonic schizophrenia being successfully treated with ECT, bilateral ECT was found to be ineffective in patients with LAOP (54, 55). These non-responders had structural brain changes on CT and MRI scans (lateral ventricular enlargement or subcortical structural changes). In addition to not being effective, ECT was not well-tolerated by patients with LAOP: they were at increased risk for inter-ictal delirium during the course of ECT (55).

In summary, bilateral ECT seems to be effective both as an acute and maintenance treatment of older patients with schizophrenia who had the onset of their illness earlier in life. ECT does not seem to be useful in those with very-late onset psychosis (64) probably due to the high prevalence of comorbid brain pathology other than schizophrenia. Other brain stimulation interventions have not been investigated in these populations. Given the significant role of cognitive function in determining real world function in patients with schizophrenia (65, 66) and the additive effect of age-related changes in cognition, it would be worth studying other ECT modalities such as right unilateral ECT and ultrabrief ECT or other brain stimulation modalities that could be pro-cognitive or at least have less cognitive adverse effects than ECT (e.g., rTMS or MST).

## CONCLUSIONS

Various brain stimulation modalities have been studied to treat older adults with non-unipolar depression, dementia, and schizophrenia. In these studies, ECT was the most common modality, followed by rTMS, VNS, and DBS. All these studies share one common limitation: a small sample size. Given the promising results of some of these studies, larger multi-center are necessary to confirm and compare the efficacy and tolerability of these various brain stimulation techniques.

In addition to small sample sizes, many studies were retrospective chart reviews and very few of the prospective studies included a control condition. It is difficult to conduct a randomized controlled trial (RCT) of ECT as illustrated by a relatively recent study that was terminated because of participants' refusal to be randomized to ECT (67). However, this study offered randomization after failing one antidepressant. Patients who have failed several medications may be more willing to participate in trials offering alternative interventions.

An optimal control intervention for rTMS studies is also yet to be identified. Sham TMS coils have been used and are better with respect to blinding than, for example, angling the coil. However, the physical sensations induced by a sham TMS coil are different than those induced by a real TMS coil. This raises the issue of whether rTMS studies should recruit only rTMS naïve participants, or whether a crossover design should be considered to ensure that all participants receive both active and sham rTMS. However, cross-over trials have their own methodological and analytical challenges. Regardless, the blinding property of a control intervention may also need to be established prior to using it in an efficacy trial.

VNS RCTs are likely to be challenging as well. The common change in voice or hoarseness during stimulation is difficult to control for. Yet, it is critical to control for such a common

and influential variable. The significant improvement observed following the VNS surgical procedure and before the onset of stimulation is also a methodological challenge consistent with the powerful placebo effect of invasive procedures. This concern also applies to other brains stimulation interventions such as DBS. Taken together, these concerns underline the need for controlled trials although the designs may need to be other than traditional parallel-group RCTs. Crossover or off-on-off-on designs may be feasible with relatively small sample sizes. They may also allow avoiding placebo-only surgical interventions while still advancing the understanding of the mechanisms of treatment. In these designs, the residual effect of the active treatment will need to be estimated. Conducting pilot studies that not only estimate the clinical efficacy but also clarify the putative mechanism could be one approach to estimate this residual effect. While changes in clinical symptoms may require large samples to characterize their timeframes, changes in underlying biological mechanisms (e.g., cortical thickness, neurophysiological markers) may be less variable and therefore easier to estimate in pilot studies.

Another approach to avoid the administration of only a placebo invasive or non-invasive intervention is to combine another active treatment with the brain stimulation intervention. For example, patients with dementia and behavioural symptoms could all receive pharmacotherapy alone for a specific period of time before being randomized to brain stimulation as an add-on. The challenge with such trial designs is that if the first intervention has a delayed effect, the effect size of the brain stimulation will end up being smaller than when used without that first intervention.

Another common limitation to the studies reviewed is the lack of long-term or even at times short-term assessment of cognition in response to various brain stimulation approaches. The association between ECT and memory impairments has been extensively studied in patients with mood disorders (68). However, it is not clear whether ECT would result in cognitive impairments or improvement in patients with dementia or schizophrenia. Some studies have suggested an improvement in cognition when ECT was used in treating depression occurring in the context of dementia. Given that individuals with dementia or schizophrenia have cognitive deficits at baseline, the cognitive impairment possibly induced by ECT may be outweighed by global improvement. In contrast, other brain stimulation modalities that could spare cognition or even improve it (e.g., MST, rTMS) may be more desirable and should be investigated with long-term assessments their effects both on symptoms and cognition.

Further, a number of advances in brain stimulation have yet to be applied to late-life severe mental illnesses. Some of these advances (e.g., ultra-brief pulse width ECT or focal ECT) are thought to enhance well-established treatments such as ECT. Others are new developments based on animal models and in vitro neuroplasticty inducing paradigms such as deep TMS, MST, paired associative stimulation, theta-burst stimulation, and transcranial direct current stimulation (tDCS). A common feature to most of these advances is that, similar to DBS, they can target specific circuitries in the brain. Further, when combined with neuroimaging or neurophysiologic tools, they could inform us of underlying changes that occur in response to an intervention. Such biologically based and circuitry specific interventions could have less cognitive adverse effects than interventions such as ECT and possibly could even enhance cognition. Further, this pro-cognitive effect could be further enhanced by combined brain stimulation with another intervention such as cognitive remediation.

Given the large number of brain stimulation modalities, the multiple variations of each modality, and the fact that some modalities are more established than others (e.g., bilateral ECT vs. MST), trials comparing one modality to another should also be considered. In such

head-to-head trials, a superiority trial is required to justify the use of a modality that is more invasive, burdensome, or costly than the other one. For example, to justify the use of MST or VNS over rTMS, a trial powered to demonstrate the superiority of MST or VNS over TMS would be needed. By contrast, when one modality is less invasive, burdensome, or costly, or associated with fewer adverse effects than another modality, a non-inferiority trial can be considered to justify the use of the more benign intervention (69). For example, trials demonstrating the non-inferiority of MST compared to ECT are needed given the expected favorable cognitive profile of MST. Defining an acceptable threshold for non-inferiority, optimal use of the standard intervention, and comparable adherence to both interventions are among the factors that should be considered when planning a non-inferiority trial.

In summary, several brain stimulation modalities show promise in the treatment of late-life psychiatric disorders other than unipolar depression. Research to characterize the dosimetry, efficacy, safety, and specific roles of these interventions is urgently needed.

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**Table 1**

Brain stimulation techniques for the treatment of non-unipolar depression in older adults.

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| **(Foster and Ries, 1988)** | To describe the clinical course of a patient with psychotic depression and essential hypertension treated with ECT. | 1 (F=1) | 74 | Psychotic depression; essential hypertension | ECT, bilateral (7 sessions) | Case report | Blood pressure | • ECT associated with significant hypertension<br>• Clonidine and hydralazine insufficient in treating post-ECT hypertension<br>• Labetalol (i.v.) effective acutely (i.v.) and orally to manage essential and ECT-induced hypertension |
| **(Tancer and Evans, 1989)** | To describe the clinical course of older adults psychotic depression treated with ECT and concurrent anticoagulation therapy. | 3 (F=1) | 69.0 (3.0) [66–72] | Psychotic depression; cardiovascular disease | ECT, bilateral (6–8 sessions) | Case series | Peak blood pressure, Prothrombin time | • All participants responded to ECT<br>• No significant adverse effects with concurrent ECT and warfarin (p.o.) treatment |
| **(Morris, 1991)** | To evaluate the use of three presumed predictors of initial response to ECT in older adults with depression: Newcastle scale, presence/absence of delusions, abbreviated Hamilton Rating Scale. | 30 (F=29) | 74 (n/a) [65–88] | Psychotic and non-psychotic depression (numbers in each group are not reported) | ECT, unknown protocol (mean 7.1 [4–14] sessions) | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: none) | MADRS | • Abbreviated Hamilton Rating Scale (initially developed in an elderly population) correlated with reduced MADRS scores<br>• No correlation between Newcastle scale and presence/absence of delusions with MADRS scores |
| **(Mulsant et al., 1991)** | To describe the effect of ECT treatment on the mood, cognition, and medical status of older adults with depression. | 40 (F=35) | 73.5 (7.3) [60–89] | MDD (n=25 including 10 with Psychotic depression). Bipolar disorder, depression (n=9). Organic mental disorder with major depressive syndrome (n=8). | ECT (8.3 (2.6) [4–13] sessions), unilateral only (n=29), bilateral only (n=3), unilateral then bilateral (n=10). | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: none) | HDRS, BPRS, MMSE | • All participants showed decreased depressive symptoms<br>• >2/3rds of participants in complete/partial remission at discharge<br>• Participants with psychotic depression had greater improvement than participants with non-psychotic depression<br>• Three participants experienced significant medical complications: syncope, symptomatic vertebral compression fractures |

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| **(Nelson et al., 1991)** | To evaluate the efficacy and safety of ECT in treating older adults with MDD and dementia. | MDD with dementia: 21 (F=14), MDD without dementia: 84 (F=58) | MDD with dementia: 75.7 (2.6) [?], MDD without dementia: 71.5 (2.9) [?] | Depression; dementia | ECT, unilateral | Retrospective chart review, 1985–1989 | Likert-type scales measuring: 1)Overall improvement, 2)Degree of dementia, 3)Post-ECT confusion, 4)Cardiac side effects | • Both groups responded to ECT<br>• Cardiac adverse effects not increased in participants with dementia compared to participants without dementia<br>• Some participants with dementia experienced transitory increased confusion |
| **(Arrsland et al., 1996)** | To describe the clinical course of an elderly patient with early-onset AD and depression treated with ECT. | 1 (F=1) | 67 | Depression; dementia (AD) | ECT, unilateral (14 sessions) | Case study | Cornell scale for depression in dementia | • Acute response to ECT<br>• Maintained with paroxetine<br>• Two subsequent relapses treated with additional ECT sessions Maintenance ECT most efficient prophylaxis |
| **(Llorente and Holland, 1996)** | To describe the clinical course of a patient with depression and previous bilateral frontal lobotomy treated with ECT. | 1 (F=1) | 89 | Psychotic depression; history of bilateral frontal lobotomy | ECT, unilateral (2 sessions/ week) | Case report | Clinical assessment | • Improvement in depressive and psychotic symptoms after 4 sessions<br>• Adverse effects (amnesia and incontinence) resolved over 4 months<br>• Symptom-free at 6-month follow-up with fluoxetine maintenance |
| **(Wesson et al., 1997)** | To evaluate the effect of age on longer-term outcomes of ECT therapy in adults with depression. | 63 (F=43) | 62 (n/a) [26–87] | Depression with melancholia or psychosis | ECT, variable protocol | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: none), mean follow-up at 35.8 months | MADRS, semi-structured interview | • Two-fold increase in likelihood of improved outcome with additional 20 years of age |
| **(Dighe-Deo and Shah, 1998)** | To describe the clinical course of two patients with depression and long bone fractures treated with ECT. | 2 (F=2) | 80.0 (5.7) [76–84] | Depression, unipolar (n=1), bipolar (n=1) | ECT, bilateral (8–9 sessions) | Case series | Clinical assessment | • Significant improvement without musculoskeletal complications in both cases |
| **(Flint and Rifat, 1998)** | To evaluate the efficacy of pharmacotherapy vs. ECT in older adults with psychotic depression. | ECT: 17 (F=10), Pharmac otherapy: 8 (F=8) | ECT: 75.7 (6.0) [60-n/a], Pharmac otherapy: 75.5 (5.1) [60-n/a] | Psychotic depression | ECT, unilateral then bilateral if no response (mean 9.9 (3.2) [4–16] sessions). Pharmacother apy. | Prospective study (Participants: non-blind, Assessors: non- | HDRS | • 25% participants responded to pharmacotherapy and 88.2% participants responded to ECT after 6 weeks |

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| | | | | | | blind, Control conditions: none) | | • Slower response time to pharmacotherapy compared to ECT |
| **(Brodaty et al., 2000)** | To evaluate the effect of age on ECT response in older adults with depression. | 81 (F=53) | <65 yrs: 53.0 (11.0) [25–64], 65–74 yrs: 69.2 (3.1), >75 yrs: 79.5 (3.6) [75–89] | Bipolar (n=14), Psychotic (n=46), Melancholia (DSM-III-R) (n=75), Melancholia (Newcastle) (n=64) | ECT, unilateral or bilateral (mean 11.3 (5.1) sessions) | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: none) | HDRS, GAF, clinical outcome rating scale | • Improvement after ECT on HDRS and clinical outcome ratings comparable for all age groups<br>• Improvements on GAF comparable post-ECT but not at follow-up; 35.7% of oldest group had dementia after 5 yrs<br>• Participants who did and did not develop dementia clinically indistinguishable prior to ECT<br>• Number and severity of adverse effects similar pre- and post-ECT, not associated with age |
| **(Rao and Lyketsos, 2000)** | To describe the impact of ECT in treating older adults with dementia and concurrent depression. | 31 (F=25) | 75.6 (9.9) [55–97] | AD (n=4), Vascular dementia (n=17), Degenerative dementia of uncertain etiology (n=10) | ECT, unilateral or bilateral (1–23 sessions) | Retrospective chart review, 1991–1996 | MADRS, MMSE, CGI | • Improved mood: MADRS mean decline of 12.3 from admission score of 27.5<br>• Most common adverse effect: delirium (49%) |
| **(Weintraub and Lippmann, 2001)** | To describe the clinical course of two patients with dementia and concurrent affective disorders treated with ECT. | 2 (F=2) | 86 (2.8) [84–88] | Depression; dementia | ECT, bilateral | Case series | Clinical assessment | • Improved depressive and manic symptoms after ECT in both cases No significant adverse effects |
| **(Rasmussen et al., 2003)** | To describe the clinical course of seven older adults with depression and suspected DLB treated with ECT. | 7 (F=5) | 73.3 (11.0) [58–90] | Depression; dementia (suspected DLB) | ECT, unilateral or bilateral (multiple sessions) | Case series | Clinical assessment | • All participants showed improvement in depressive symptoms post-ECT<br>• Maintenance ECT associated with stabilization of mood disorder without cognitive worsening<br>• Rapid relapse common |
| **(Janakirama n et al., 2006)** | To describe the clinical course of a patient with depression treated with ECT who experienced musical hallucinations. | 1 (F=1) | 93 | Psychotic depression | ECT, bilateral (8 sessions) | Case report | Clinical assessment | • Resolution of depression following full course of ECT |

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | • Adverse effects included musical hallucination with initiation of ECT |
| **(Suzuki et al., 2006)** | To describe the clinical course of a patient with depression treated with ECT and maintenance ECT. To correlate improvement in symptoms achieved with maintenance ECT and resolution of cerebral hypoperfusion. | 1 (F=1) | 70 | Psychotic depression | ECT, bilateral, maintenance | Case report | MMSE, cerebral perfusion (single photon emission CT) | • Patient successfully treated with maintenance ECT for 4 years at time of publication<br>• Cerebral hypoperfusion persisted despite response to first course of acute ECT<br>• Relapse occurred 2 weeks later<br>• Cerebral hypoperfusion improved after response to second course of acute ECT<br>• Perfusion normalized after 2-year maintenance ECT |
| **(Buhl et al., 2007)** | To describe the clinical course of a patient with depression treated with ECT and maintenance-ECT. | 1 (F=1) | 89 | Psychotic depression | ECT, bilateral, maintenance (172 sessions) | Case report | Clinical assessment | • Maintenance ECT effective and well-tolerated over 9 year period without concurrent antidepressant treatment<br>• Patient capable o self-care and independent<br>• No major depressive episodes or residual symptoms<br>• No significant confusion or memory impairment |
| **(Jorge et al., 2008)** | To evaluate the efficacy and safety of rTMS in treating older adults with vascular depression. | Study 1: TCD-12K (n=15, F=6), Sham (n=15, F=8). Study 2: TCD-18K (n=33, F=20), Sham (n=29, F=17). | Study 1: TCD-12K (62.9 (7.2)), Sham (66.1 (11.0)). Study 2: TCD-18K (64.3 (9.4)), Sham (62.1 (8.5)) | Vascular depression, i.e. depressive disorders with clinical evidence of cerebrovascular disease. | rTMS; Patients randomly assigned to receive active or sham rTMS of the left dorsolateral prefrontal cortex | Randomized prospective study (Participants: blind, Assessors: blind, Control conditions: active and sham rTMS) | HDRS | • Study 1:<br>• % Decrease in HDRS scores: Sham group 13.6%, TCD-12K group 33.1% (P=0.04)<br>• Response rates: Sham group 6.7%, TCD-12K group 33.3% (P=0.08)<br>• Remission rates: Sham group 6.7%, TCD-12K group 13.3% (P=0.50)<br>• Study 2:<br>• % Decrease in HDRS scores: Sham group 17.5%, TCD-18K group 42.4% (P=0.001) |

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | • Response rates: Sham group 6.9%, TCD-18K group 39.4% (P=0.003)<br>• Remission rates: Sham group 3.5%, TCD-18K group 27.3% (P=0.01)<br>• Response rates negatively correlated with age and smaller frontal gray matter volumes<br>• Common adverse effects: headache, local discomfort |
| **(Lyons and Symon, 2008)** | To describe the clinical course of a patient with depression treated with ECT while on venlafaxine. | 1 (F=1) | 84 | Psychotic depression | ECT, unknown protocol (48 sessions in total) | Case report | Clinical assessment | • Two episodes of asystole while on venlafaxine during ECT<br>• Four relapses over three years; each treated successfully with ECT (10–14 sessions)<br>• 48 ECT treatments in total with two episodes of asystole, both during her fourth ECT course and while on venlafaxine: first asystole while on 150 mg venlafaxine, second asystole while on 75 mg venlafaxine |
| **(Navarro et al., 2008)** | To evaluate the efficacy and safety of continuation-maintenance ECT in treating elderly patients with psychotic depression after acute ECT remission. | Nortripty line: 17 (F=11), ECT/nort riptyline: 16 (F=10) | Nortripty line: 70.7 (3.4), ECT/Nor triptyline: 70.4 (3.2) | Psychotic depression | ECT, bilateral, maintenance | Randomized prospective study (Participants: non-blind, Assessors: blind, Control conditions: none) | HDRS, Newcastle Scale | • Significantly longer mean survival time until relapse in combined ECT plus nortriptyline group (23 months) than in the nortriptyline alone group (16 months) at two year follow-up<br>• No differences in tolerability between groups |
| **(Fazzari et al., 2009)** | To describe the clinical course of a patient with frontotemporal atrophy and Cotard's delusions treated with bilateral ECT for depression. | 1 (F=0) | 69 | Depression; dementia | ECT, bilateral (6 sessions) | Case report | BPRS, HDRS, HARS, GAF, CGI | • Improved mood, increased cognitive performance, and remission of anxiety post-ECT<br>• Improvement persisted at one month follow-up |
| **(Takahashi et al., 2009)** | To evaluate the efficacy and safety of TMS and ECT in treating depression accompanying DLB. To describe the | DLB: 23 (F=17), Non-DLB: 144 (F=92) | DLB: 63.5 (9.2), Non-DLB: 63.2 (9.0), Overall: 63 (9) [50–83] | DLB (concurrent MDD: n=22, bipolar: n=1). Non-DLB (concurrent mood disorders) | ECT, bilateral (DLB participants treated: 8 (F=7), age: 71.6 (7.3)). TMS (DLB participants treated: 6 (F=3), age: 61.9 (9.2)) | Prospective pilot study (Participants: non-blind, Assessors: non- | HDRS | • Significant improvement in HDRS scores of DLB group post-ECT (38.0 to 15.0) and TMS (24.0 to 11.0) |



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| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| | characteristic depressive symptoms during the prestage, i.e. mood disorder without dementia or prodromal phase of DLB. | | | | | blind, Control conditions: none) | | • Adverse effects: dysfunction of autonomic nervous system in DLB group |
| **(Cohen et al., 2010)** | To describe clinical and demographic predictors of length of rTMS treatment for remission in older adults with bipolar depression. | 56 (F=30) | 48 (15) [?] | Bipolar depression | rTMS (up to 30 sessions) | Retrospective chart review, 2000–2006 | HDRS | • Age, refractoriness, number of prior depressive episodes, and severe depression at baseline associated with longer rTMS treatment<br>• Adverse effects: somnolence (n=2), headache (n=6), nightmares (n=3) |
| **(Hausner et al., 2011)** | To study cognitive performance in depressed geriatric inpatients with or without pre-existing cognitive impairment who received a first course of ECT. | 44 (F=33) | 73 (6) [65–89] | MDD with NCI (n=13), MCI (n=19), dementia (n=12) | ECT, unilateral or bilateral (6 sessions) | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: none) | HDRS | • Remission of affective symptoms in all groups as measured by HDRS-21<br>• Non-significant cognitive decline in all groups after initial ECT<br>• Cognitive improvement in NCI and MCI groups 6 weeks and 6 months post-ECT<br>• Cognitive improvement in participants with dementia on anti-dementia treatment after last ECT session; cognitive deterioration in participants with dementia not on anti-dementia treatment<br>• Cognitive decline in 70% of dementia participants and 68.8% of MCI participants 6 weeks after last ECT session; decline remained in 33% of dementia participants 6 months after last ECT session |

Alzheimer's Disease (AD), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions (CGI), Dementia with Lewy Bodies (DLB), Electroconvulsive Therapy (ECT), Global Assessment of Functioning (GAF), Hamilton Anxiety Rating Scale (HARS), Hamilton Depression Rating Scale (HDRS), Major Depressive Disorder (MDD), Mild Cognitive Impairment (MCI), Mini Mental State Examination (MMSE), Montgomery Asperg Depression Rating Scale (MADRS), No Cognitive Impairment (NCI), Repetitive Transcranial Magnetic Stimulation (rTMS), Transcranial Magnetic Stimulation (TMS), Total Cumulative Dose (TCD)

**Table 2**

Brain stimulation techniques for the treatment of dementia in older adults.

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| **(Mulsant et al., 1991)** (also reported in Table 1) | To describe the effect of ECT treatment on the mood, cognition, and medical status of older adults with depression. | 40 (F=35) | 73.5 (7.3) [60–89] | MDD (n=25 including 10 with Psychotic depression). Bipolar disorder, depression (n=9). Organic mental disorder with major depressive syndrome (n=8). | ECT (8.3 (2.6) [4–13] sessions), unilateral only (n=29), bilateral only (n=3), unilateral then bilateral (n=10). | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: none) | HDRS, BPRS, MMSE | • In addition to what is reported in Table 1, most patients, especially those with dementia (N = 8), experienced a significant increase in MMSE,<br>• 13 out of the 40 patients experienced confusion between ECT sessions.<br>• MMSE did not predict confusion |
| **(Rao and Lyketsos, 2000)** (also reported in Table 1) | To describe the impact of ECT in treating older adults with dementia and concurrent depression. | 31 (F=25) | 75.6 (9.9) [55–97] | AD (n=4), Vascular dementia (n=17), Degenerative dementia of uncertain etiology (n=10) | ECT, unilateral or bilateral (1–23 sessions) | Retrospective chart review, 1991–1996 | MADRS, MMSE, CGI | • In addition to what is reported in Table 1, there was improvement in cognition: MMSE mean increase of 1.62 points from admission score of 18.8 |
| **(Grant and Mohan, 2001)** | To describe the clinical course of four older adults with dementia treated with ECT for agitation and aggression. | 4 (F=3) | 72.3 (10.8) [56–78] | AD (n=2). Dementia, unclassified (n=2) | ECT | Case series | Clinical assessment | • Improvement in symptoms associated with dementia<br>• Effects lasted 3 to 12 months after 2–4 ECT sessions |
| **(McDonald and Thompson, 2001)** | To describe the treatment of mania in conjunction with dementia in older adults with ECT | 3 (F=?) | older adults | Mania, dementia | ECT, unilateral (short course followed by maintenance ECT) | Case series | Clinical assessment | • Improvement in symptoms of mania and agitation<br>• Improved cognition |
| **(Sjogren et al., 2002)** | To evaluate the cognitive-enhancing effects of VNS | 10 (F=8) | 67 (7.6) [57–78] | AD, probable | VNS | Prospective pilot study (Participants: blind during 2 | Alzheimer's Disease Assessment Scale-cognitive (ADAS-Cog), MMSE, | • 3 months post-VNS: 7/10 participants responded to treatment as |

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| | in treating older adults with AD. | | | | | week surgical recovery period, Assessors: non-blind, Control conditions: none) | Gottfries-Brane-Steen scale, CGI | measured by ADAS-Cog (median improvement of 3 points) and 9/10 participants responded to treatment as measured by MMSE (median improvement of 1.5 points)<br>• 6 months post-VNS: 7/10 participants responded to treatment as measured by ADAS-Cog and MMSE<br>• Adverse effects mild and transient |
| **(Cotelli et al., 2006)** | To assess the effect of rTMS applied to the dorsolateral prefrontal cortex on picture naming in older adults with mild to moderate AD. | 15 (F=?) | 76.7 (6.0) | AD, probable | rTMS (1 × 600 ms at 20 Hz) | Experimental study (Participants: blind, Assessors: non-blind, Control conditions: left, right, and sham rTMS) | Action-object picture naming task (Center for Research in Language International Picture Naming Project) | • Study made up of three experimental blocks: left, right, and sham rTMS stimulation<br>• Improved action naming with right and left-sided rTMS |
| **(Merrill et al., 2006)** | To evaluate the cognitive-enhancing effects of VNS in treating older adults with AD at one year. | 17 (F=11) | 63 (n/a) [57–81] | AD, probable | VNS | Prospective pilot study (Participants: blind during 2 week surgical recovery period, Assessors: non-blind, Control conditions: none) | ADAS-Cog, MMSE | • 7/17 participants improved or did not decline as measured by ADAS-Cog after one year<br>• 12/17 participants improved or did not decline as measured by MMSE after one year<br>• No significant changes in median scores<br>• No significant decline in mood, behaviour, or quality of life after one year<br>• Most common adverse effect: voice |



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| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | alteration or hoarseness |
| **(Katagai et al., 2007)** | To describe the clinical course of a patient with dementia with psychotic feature treated with ECT. | 1 (F=1) | 92 | Dementia, cerebrovascular with psychotic feature | ECT, bilateral (2 sessions) | Case study | Behave-AD | • Experienced QTc prolongation while treated with haloperidol (0.5 mg, i.v.)<br>• Almost all psychotic symptoms resolved after first session of ECT<br>• No cognitive adverse effects observed |
| **(Cotelli et al., 2008)** | To assess the effect of rTMS applied to the dorsolateral prefrontal cortex on picture naming in older adults with mild or moderate-severe AD. | 24 (F=?) | Mild AD: 75.0 (6.2), Moderate-severe AD: 77.6 (5.8) | AD, probable | rTMS (1 × 600 ms at 20 Hz) | Experimental study (Participants: blind, Assessors: non-blind, Control conditions: left, right, and sham rTMS) | Action-object picture naming task (Center for Research in Language International Picture Naming Project) | • Study made up of three experimental blocks: left, right, and sham rTMS stimulation<br>• Mild AD group (MMSE 17–30): improved action but not object naming with right and left-sided rTMS<br>• Moderate-severe AD group (MMSE 0–16): improved action and object naming with right and left-sided rTMS |
| **(Laxton et al., 2010)** | To investigate possible clinical benefits of DBS in older adults with AD by: 1) mapping brain areas whose physiological function are modulated by stimulation, (2) assessing whether DBS can correct regional alterations in | 6 (F=2) | 60.7 (6.1) [51–69] | AD, probable | DBS | Prospective pilot study (Participants: non-blind, Assessors: non-blind, Control conditions: none) | ADAS-Cog, MMSE | • Improvement or slowing in symptoms of AD as measured by ADAS-Cog and MMSE at 6 and 12-month follow-up post-DBS in some participants<br>• PET scans showed reversal of impaired glucose metabolism in the temporal and parietal lobes; maintained after 12 months of DBS |

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| | cerebral glucose metabolism, and 3) measuring the effects of DBS on cognition over time. | | | | | | | • No serious adverse events reported. |
| **(Bentwich et al., 2011)** | To evaluate the efficacy of combination high-frequency repetitive TMS and cognitive training (rTMS-COG) in treating patients with AD. | 8 (F=2) | 75.4 (4.4) [69–80] | AD, probable | Intensive treatment (int-rTMS-COG): 5 sessions/wk for 6 wks. Maintenance (maint-rTMS-COG): 2 sessions/wk for 12 wks. | Prospective pilot study (Participants: non-blind, Assessors: non-blind, Control conditions: none) | ADAS-Cog, CGI, MMSE, ADAS-ADL, HDRS, NPI | • ADAS-Cog scores improved by 4 points after both 6 weeks and 4.5 months<br>• CGI scores improved by 1.0 after 6 weeks and 1.6 points after 4.5 months<br>• MMSE, ADAS-ADL, and HDRS scores did not show statistically significant improvement<br>• NPI test scores did not change<br>• No adverse effects recorded |
| **(Cotelli et al., 2011** | To evaluate the long-term effect of rTMS applied to the left dorsolateral prefrontal cortex on cognitive performance in patients with AD. | 10 (F=?) | Real-real 71.2 (6.1); Sham-real 74.4 (3.8) | AD, probable | rTMS real-real (n=5), sham-real (n=5) (4 weeks, 5 sessions/wk) | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: sham-real treatment group) | MMSE, Picture Naming Task, Battery for Analysis of Aphasic Deficits | • Significantly improved auditory sentence comprehension in real-real group compared to the sham-real group and baseline<br>• No adverse effects recorded |
| **(Hausner et al., 2011)** (also reported in Table 1) | To study cognitive performance in depressed geriatric inpatients with or without pre-existing cognitive impairment who received a first course of ECT. | 44 (F=33) | 73 (6) [65–89] | MDD with NCI (n=13), MCI (n=19), dementia (n=12) | ECT, unilateral or bilateral (6 sessions) | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: none) | HDRS | • Remission of affective symptoms in all groups as measured by HDRS-21<br>• Nonsignificant cognitive decline in all groups after initial ECT<br>• Cognitive improvement in NCI |

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | and MCI groups 6 weeks and 6 months post-ECT<br>• Cognitive improvement in participants withdementia on anti-dementia treatment after last ECT session; cognitive deterioration in participants with dementia not on anti-dementia treatment<br>• Cognitive decline in 70% of dementia participants and 68.8% of MCI participants 6 weeks after last ECT session; decline remained in 33% of dementia participants 6 months after last ECT session |
| **(Ujkaj et al., 2012)** | To evaluate the safety and efficacy of ECT for agitation and aggression associated with dementia. | 16 (F=15) | 66.6 (8.3) [51–79] | AD (n=8), Vascular dementia (n=2), Frontotemporal dementia (n=3), Other dementia (n=3) | ECT, unilateral then bilateral if insufficient response (9 sessions) [2–15] | Retrospective systematic chart review | Pittsburgh Agitation Scale, CGI, GAF | • Significant decrease in agitation<br>• 15/16 participants showed improvement |

Alzheimer's Disease (AD), Alzheimer's Disease Assessment Scale-cognitive (ADAS-Cog), Alzheimer's Disease Assessment Scale-activities of daily living (ADAS-ADL), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions (CGI), Deep Brain Stimulation (DBS), Electroconvulsive Therapy (ECT), Global Assessment of Functioning (GAF), Mini Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), Vagus Nerve Stimulation (VNS)

**Table 3**

Brain stimulation techniques for the treatment of schizophrenia in older adults.

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| **(Botteron et al., 1991)** | To describe the clinical course and brain imaging findings of older adults with late age onset psychosis receiving ECT. | 3 (F=3) | 76 (4.4) [71–79] | Late age onset psychosis. | ECT, bilateral | Case series | Clinical assessment | • Pre-existing brain changes present in all three cases<br>• No response to ECT in the two patients with more severe structural changes (lateral ventricular enlargement, deep-white-matter hyperintensities) |
| **(Figiel et al., 1992)** | To describe the clinical course and brain imaging findings of older adults with late age onset psychosis receiving ECT. | 6 (F=6) | 75 (8.2) [65–89]; Age of onset 73 (8.6) [65–89] | Late age onset psychosis. | ECT, bilateral | Case series | Clinical assessment | • 5/6 patients did not respond to ECT<br>• One or more structural brain changes (lateral ventricular enlargement, subcortical structural changes) present in all non-responders<br>• Higher risk for interictal ECT-induced delirium in older patients with late age onset psychosis |
| **(Kramer, 1999)** | To describe the clinical course of five older adults with schizophrenia or schizoaffective disorder receiving ECT. | 5 (F=5) | 65 (6.7) [58–74] | Schizophrenia, chronic undifferentiated (n=1). Schizoaffective disorder. | ECT, bilateral | Case series | Clinical assessment | • Improved psychosis in all cases<br>• Four patients responded to combination ECT and antipsychotics<br>• One patient responded to ECT without antipsychotics |

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | (patient refused pharmacotherapy) |
| **(Suzuki et al., 2003)** | To evaluate the efficacy of acute ECT in treating older adults with catatonic schizophrenia. | 9 (F=6) | 63 (12.7) [45–77] | Schizophrenia, catatonic. | ECT, bilateral (12 sessions) | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: none) | BPRS GAF, Guy's five factors | • Response to treatment in all participants as measured by improvement in BPRS, GAF, and Guy's five factors<br>• One case of supraventricular premature contractions during ECT seizure<br>• Three cases of mild-moderate post-ECT delirium 6that resolved within 3 days |
| **(Suzuki et al., 2004)** | To evaluate the efficacy of acute ECT and continuation antipsychotics in treating and preventing relapse of older adults with catatonic schizophrenia. | 11 (F=8) | 62 (12.1) [45–77] | Schizophrenia, catatonic. | ECT, bilateral (12 sessions). Continuation antipsychotics. | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: none). | BPRS GAF, Guy's five factors | • All participants completed phase I (acute ECT) and phase II (continuation antipsychotics) studies<br>• 7/11 participants relapsed within 6 months while receiving continuation antipsychotics |
| **(Suzuki et al., 2005)** | To evaluate the efficacy of continuation ECT and antipsychotics in preventing relapse in older adults with catatonic schizophrenia. | 12 (F=7) | 48 (15.9) [18–74] | Schizophrenia, catatonic (n=9), disorganized (n=1), paranoid (n=1). Schizophrenifor m disorder (n=1). | Combined continuation ECT and antipsychotics. | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: none). | BPRS GAF, Guy's five factors | • Participants were the twelve individuals who relapsed despite use of continuation antipsychotics within 6 months after responding to two acute courses of ECT |

| Publication | Aim | Subjects (n, sex) | Age (Mean (StdDev) [Range]) | Diagnosis | Technique | Method | Outcome Measures | Findings |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | • 3/12 participants relapsed<br>• Time to relapse in this phase 3 study (continuation ECT combined with antipsychotics) significantly longer than in phase 2 (continuation antipsychotics only): 153.0 (30.0) and 63.7 (55.7) days respectively, P<0.01 |
| **(Suzuki et al., 2006)** | To evaluate the effect of adjusting the frequency of continuation and maintenance ECT on older adults with catatonic schizophrenia who relapsed during combined continuation ECT and antipsychotics. | 3 (F=2) | 61 (12.5) [49–74] | Schizophrenia, catatonic. | ECT, bilateral | Prospective study (Participants: non-blind, Assessors: non-blind, Control conditions: none). | BPRS, GAF, Guy's five factors | • All participants responded to third course of acute ECT<br>• Remission (no relapse in more than six months) achieved with increased frequency of continuation ECT and subsequent maintenance ECT<br>• No severe adverse effects reported. |

Brief Psychiatric Rating Scale (BPRS), Electroconvulsive Therapy (ECT), Global Assessment of Functioning (GAF)