Cognitive Adverse Effect of Electroconvulsive Therapy: Is It Preventable?

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ABSTRACT

Introduction: Electroconvulsive therapy (ECT) has been widely accepted as among the most effective therapeutic methods for major depressive disorder (MDD) or schizophrenia patients who show poor response to standard pharmacological treatment. One of the adverse effects of ECT which remains controversial is cognitive impairment.

Methods: In this article, we review the available literature about pharmacological agents that could prevent the cognitive adverse effects of ECT.

Results: Among the agents that have been shown to prevent cognitive adverse effects of ECT in humans include piracetam, naloxone, anesthetic agents, anticholinesterase drugs, memantine, thyroid hormones, and a combination of herbs.

Conclusion: While preventing the cognitive adverse effects of ECT is currently not attainable, using pharmacological agents/herbs have been found to confer beneficial effects in reducing cognitive impairment.

KEY WORD

electroconvulsive therapy, cognitive impairment, pharmacological agent, animal studies, clinical studies

INTRODUCTION

Electroconvulsive therapy (ECT) is a brief, non-invasive peripheral electrical stimulation procedure used to produce a generalized seizure. It is used throughout the world as one of the most effective therapeutic methods for treatment-resistant mental disorders, especially, major depressive disorder (MDD) and schizophrenia. Although ECT has been widely accepted as one of the most effective treatment modalities for certain psychiatric conditions, its mechanisms of action remain elusive. Several theories have been put forward in attempts to explain its mechanism of action.

Adverse effects of ECT are usually minor, self-limiting, and can be symptomatically managed. General adverse effects following ECT include dry mouth, nausea, headache, and myalgia. Figure 1 summarizes the possible aetiologies of ECT's adverse effects. However, the adverse effects of ECT on cognitive function remain at the root of much controversy.

The cognitive adverse effects of ECT can be divided into nonmemory and memory. There are continuing discussions about the extent to which they persist. The identification and assessment of cognitive adverse effects are confounded by many variables such as severity and nature of the psychiatric disorder, nature, and dose of concurrent psychotropic medication, nature and dose of ECT premedication, degree of residual psychiatric impairment after ECT, and specific ECT technique used.

The nonmemory cognitive adverse effects of ECT include impairment in executive function, including reasoning, concentration, organizational skill deficit, loss of reasoning ability, and loss of intelligence. These effects are substantial, although not larger than the effects of depression. In certain studies, however, the nonmemory cognitive functions were even improved during ECT and post ECT. The improvement could be attributed to various factors such as the ECT itself, effects of other prescribed drugs, improvement of illness which might have caused the temporary nonmemory cognitive impairment, or a natural course in the progression of the mental illness.

There are four recognized types of memory cognitive adverse effects of ECT. Post-ictal confusion occurs immediately following an ECT treatment, retrograde and anterograde amnesia which occur after clearing of the post-ictal confusion, and longer-lasting subjective memory impairment which occurs in a minority of patients. Among these, the commonest complaints from post-ECT patients are retrograde amnesia and loss of autobiographic and public events memory. Over one to six months after ECT, anterograde and retrograde amnesia generally decreases. In some cases, the acquisition and retention of new memories and long term memory are not persistently impaired, although some specific memories of events during the months before and after the ECT may be permanently lost.

MacQueen et al. however suggested that sustained learning and memory impairment may occur in bipolar patients who have had ECT compared to those who had not undergone ECT. The ECT group performed poorly on immediate, short- and long-delay free recall and cued recall measures on the California Verbal Learning Test (CVLT) than the non-ECT group. They also had further difficulties in encoding and retrieving information, implicating medial temporal lobe structures, and possibly pre-frontal cortex areas.

Subjective memory worsening following ECT has been reported in a minority of patients. In some cases, this may be explained by increased awareness of essentially normal forgetfulness, remaining psychopathology, or secondary gains associated with memory loss complaints. Nevertheless, the basis of memory complaints is not fully understood, and it is plausible that subtle persistent, though genuine, memory difficulties may go undetected by the existing neuropsychological instruments.
Table 1: Selected pharmacological agents used to prevent cognitive adverse effects of ECT in human

<table>
<thead>
<tr>
<th>Study design</th>
<th>Subjects (n)</th>
<th>ECT technique</th>
<th>Agent/dose</th>
<th>Cognitive tests</th>
<th>Time of cognitive assessment</th>
<th>Main findings</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Randomized and controlled clinical trial</td>
<td>30 patients</td>
<td>Not available</td>
<td>Piracetam 5 g IV</td>
<td>Wechsler memory test</td>
<td>Before first ECT and 3 days after the last ECT</td>
<td>Piracetam improved total memory scores compared to pre-ECT testing</td>
<td>(39)</td>
</tr>
<tr>
<td>Placebo-controlled, randomized, within-subject study</td>
<td>16 patients</td>
<td>Bilateral ECT</td>
<td>Naloxone IV 0.6 mg/kg (low dose), 1.6 mg/kg (high dose) or saline IV (placebo)</td>
<td>MMSE</td>
<td>Before the first ECT and within two days after the last ECT</td>
<td>High dose naloxone resulted in significant reductions in anterograde amnesia and better performance on an attention task. Both low and high dose naloxone improved verbal fluency.</td>
<td>(40)</td>
</tr>
<tr>
<td>Randomized, double-blind, crossover study</td>
<td>15 patients</td>
<td>Right unilateral ECT</td>
<td>Mean dose Propofol 1.9 ± 0.4 mg/kg and mean dose thiopental 3.0 ± 0.6 mg/kg</td>
<td>1. RAVLT and delayed recall 2. Simple reaction 3. Choice reaction time 4. Finger tapping time 5. Card sorting 6. Trail making test A and B</td>
<td>45 minutes after injection of the anaesthetic drugs</td>
<td>Propofol resulted in significant reductions in cognitive impairments in the early recovery period after ECT when compared to thiopental anaesthesia</td>
<td>(45)</td>
</tr>
<tr>
<td>Triple blind randomized controlled trial</td>
<td>45 patients</td>
<td>Not available</td>
<td>Donepezil, 5 mg dose (orally) started 2 days before ECT and was continued for 3 days after the last ECT</td>
<td>MMSE</td>
<td>After immediate recovery from anesthesia, and every 5-minute interval until 90 minutes</td>
<td>Donepezil resulted in more rapid recovery of various components of cognition when compared to those without donepezil</td>
<td>(59)</td>
</tr>
<tr>
<td>Pilot study</td>
<td>17 patients</td>
<td>Right unilateral ECT</td>
<td>Galantamine 4 mg bid</td>
<td>Modified MMSE</td>
<td>24 h before first ECT and 24-48 h after the last ECT</td>
<td>Galantamine significantly improved delayed memory and abstract reasoning</td>
<td>(61)</td>
</tr>
<tr>
<td>Case Report</td>
<td>One case</td>
<td>Bitemporal ECT</td>
<td>Donepezil 5 mg/d for first 2 days, and subsequently 10 mg/d</td>
<td>1. RAVLT 2. Rey-Osterrieth Complex Figure Test.</td>
<td>Before the first ECT and 7 days after ECT</td>
<td>Donepezil significantly improved both verbal and nonverbal memory when compared to baseline</td>
<td>(60)</td>
</tr>
<tr>
<td>Randomized double-blind clinical trial</td>
<td>74 patients</td>
<td>Bitemporal ECT</td>
<td>Combination capsules contained 500 mg CR, 30 mg CS, and 5 g honey</td>
<td>ACE-R</td>
<td>Before first ECT, after the fourth ECT session, following the last ECT and 1-2 months after the last ECT</td>
<td>Combined herbal treatment improved memory (minimum 1-2 months after treatment initiation)</td>
<td>(80)</td>
</tr>
</tbody>
</table>
There are several limitations concerning the studies of cognitive adverse effects of ECT25. Among these are the logistics of approaching patients for follow-up assessments, to test memory function systematically, and the inability to conduct pre-ECT cognitive assessments for comparison because of the nature of patients who are referred for ECT. These patients were too uncooperative by way of catatonic symptoms, refusing oral intake, being violent, or refusing to simply sit for a long while for completing assessments.

A recent systematic review26 revealed no changes27-30 or even improvement31,32 in the cognitive functions when compared between pre- and post-ECT for schizophrenia. Similarly, Ziegelmayer et al.33 reported no changes in cognitive performance following ECT for treatment-resistant major depression patients. An earlier meta-analysis34 revealed poor performance on several cognitive tests is limited only to the first few days post-ECT. The cognitive performance tends to improve when the same tests were repeated 2 weeks or more after the last session in depressed patients receiving ECT. Degree of impairment, recovery, and improvement from baseline over time varied for each cognitive variable across cognitive domains34. Additionally, a few case reports revealed no evidence of progressive decline in the Mini-Mental State Examination (MMSE) performance35-37.

Pharmacological agents to prevent or reduce cognitive adverse effects of ECT

An earlier review concluded inconclusive results regarding the clinical utility of pharmacological agents in preventing the cognitive effects of ECT38. Table 1 summarizes some of the pharmacological agents used to prevent the cognitive adverse effects of ECT in humans.

### Table 1: Pharmacological Agents Used to Prevent Cognitive Adverse Effects of ECT

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Patients</th>
<th>Side of ECT</th>
<th>Pharmacological Agent</th>
<th>Timing</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled clinical trial</td>
<td>63 patients</td>
<td>Not available</td>
<td>Memoral herbal capsules</td>
<td>Before first ECT and 2 months after the last ECT</td>
<td>Memoral herbal group scored higher in attention and orientation, verbal fluency and memory subscales</td>
</tr>
<tr>
<td>Randomized double-blind placebo-controlled trial</td>
<td>30 patients</td>
<td>Right unilateral ECT</td>
<td>Galantamine increased by 4 mg every 3 days to a target dose of 8 mg twice daily</td>
<td>Before first ECT and 24-48 hours after last ECT</td>
<td>Galantamine group scored significantly higher for delayed memory, at discharge</td>
</tr>
<tr>
<td>Randomized, double-blind clinical trial</td>
<td>29 patients</td>
<td>Bilateral ECT</td>
<td>Ketamine 1 - 2 mg/kg or thiopental 2 - 3 mg/kg</td>
<td>Before first ECT, 48 hours after first ECT, 3 to 7 days, and 1 month after the sixth ECT</td>
<td>Ketamine group improved cognitive function after the first ECT</td>
</tr>
<tr>
<td>Randomised placebo-controlled trial</td>
<td>40 patients</td>
<td>Not available</td>
<td>Memantine (5 mg/day) starting the day before ECT and continuing until the fourth session of ECT</td>
<td>Before first ECT, and 24 h after the last ECT</td>
<td>Memantine group scored significantly higher in recent memory at the end of ECT sessions than the control group</td>
</tr>
<tr>
<td>Double-blind clinical trial</td>
<td>60 patients</td>
<td>Bilateral ECT</td>
<td>Liothyronine 50 mcg every morning</td>
<td>Before first ECT and two months after the last ECT</td>
<td>Liothyronine group showed higher mean scores in delayed recall, verbal memory, visual memory, general memory, and attention/concentration scales</td>
</tr>
<tr>
<td>Case series</td>
<td>3 cases</td>
<td>Right unilateral ECT (except case 2, bilateral ECT)</td>
<td>Rivastigmine 4.6 mg/24 h transdermally</td>
<td>2 and 5 weeks after ECT, respectively</td>
<td>Rivastigmine improved cognitive functioning</td>
</tr>
</tbody>
</table>

MMSE: Mini-Mental State exam; RAVLT: Rey Auditory Verbal Learning Test; ACE-R: Addenbrooke's Cognitive Examination-Revised; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; WMS-R: WechslerMemory Scale-Revised
rograde memory impairments were improved with naloxone treatment\(^{40}\). That study showed significant reductions in anterograde amnesia when high dose naloxone was administered immediately before ECT but not retrograde amnesia, and better performance on an attention task\(^{40}\).

### Anaesthetic agents

It has been shown that the type of anesthetic agent used during ECT could help to reduce cognitive impairments after ECT. Ketamine revealed to be more superior than methohexital\(^{41}\), etomidate\(^{42}\), and thio- pental\(^{43,44}\) to reduce the cognitive adverse effect of ECT. However, in another study, a reduction in cognitive impairments during the early recovery period after ECT in patients who received propofol compared to thiopental anesthesia\(^{45}\). Propofol or thiopental was given alternately during ECTs and 45 minutes after each ECT, immediate and delayed verbal memory, motor speed, reaction speed, visuospatial, and executive functions were assessed\(^{45}\).

Propofol at a dose of 100 or 150 mg/kg was found to induce amnesia\(^{46}\), and its nonsedative dose (9 mg/kg) was also found to cause memory impairment in rodents\(^{46}\). Nevertheless, Lee et al.\(^{48}\) found that spatial memory was not impaired after propofol anesthesia in aged rats. In contrast, Luo et al.\(^{49}\) reported that propofol attenuates ECS-induced learning and memory impairment. A similar decrease in seizure durations but no aggravation in learning and memory deficits were observed in ECS rats pre-treated with propofol or pentobarbital sodium as compared with those pretreated with normal saline. Propofol reduced learning and memory impairment, blocked excessive expression of glutamic acid decarboxylase 65 (GAD 65), and restored the imbalance ratio of glutamate and GABA in the hippocampus induced by ECS in depressed rats.

### Thyroid hormones

Several studies examined the effects of liothyronine alone or in comparison with other agents on the memory of patients who received ECT\(^{50-55}\). Higher mean scores in delayed recall, verbal memory, visual memory, general memory, and attention/concentration scales were noted in liothyronine group than the control group\(^{55}\). The proposed mechanism derived from the animal study includes the neuroprotective effect of triodothyronine\(^{46}\). Moreover, exogenous liothyronine may suppress the anticonvulsive effect of thyrotropin-releasing hormone (TRH)\(^{52,53}\). As a result, lower required doses of electroshock and consequently decrease damage and cognitive adverse effects\(^{56}\).

### Anticholinesterase

Prakash et al.\(^{59}\) conducted a trial on two groups of patients. One group received ECT with placebo, whereas the other group received ECT and donepezil. More rapid post-ECT recovery of various cognitive components was observed in patients receiving donepezil as compared to those without donepezil. Later, Roa et al.\(^{60}\) reported a case of cognitive deficits associated with maintenance ECT which was successfully treated with donepezil. The patient was diagnosed to have paranoid schizophrenia and had a poor response after adequate trials of 3 antipsychotic drugs and experienced unbearable side effects with clozapine. The patient presented with new complaints suggestive of verbal and nonverbal memory deficits after 6 months of bitemporal ECTs maintenance. The patient was started on donepezil 5 mg/d for 2 days, the dose was subsequently increased to 10 mg/d, and maintained on this dose throughout the ECT regime. Maintenance ECT was administered to the patient three days after being started on donepezil. A marked improvement in memory (both verbal and nonverbal) was observed after starting on donepezil and was attributed to the involvement of cholinergic mechanisms.

A study on galantamine, another type of anticholinesterase, was conducted by Matthews et al.\(^{61}\). They found that patients on galantamine required fewer ECT treatments as compared to patients, not on galantamine. Delayed memory\(^{61,62}\) and abstract reasoning\(^{61}\) were significantly better following ECT in patients who received galantamine. The dual mechanism of action of galantamine includes a reversible competitive inhibition of acetylcholinesterase and allosteric modulation of nicotinic acetylcholine receptors\(^{61}\). It has been hypothesized that galantamine may reduce cognitive impairment and enhance the antidepressant action of ECT.

Rivastigmine was also reported to improve cognitive function, in particular, a decline of confusional symptoms following ECT\(^{64}\). The cholinergic system plays a significant role in the fundamental processing of attention and concentration, flexibility and speed of information gathering\(^{66}\), while reduced cholinergic neurotransmission has been shown to induce delirium\(^{66}\). Thus, rivastigmine, an acetylcholinesterase inhibitor, may improve confusional or delirious-like symptoms induced by ECT via these mechanisms.

### Memantine

The NMDA receptor has been the most extensively studied and the most frequently implicated in central nervous system diseases\(^{67}\). A hypothesis involving glutamate and the NMDA receptor in ECT-induced
memory impairment has been put forward by Chamberlain and Tsai40. There are a few studies exist on the efficacy of NMDA antagonists especially ketamine (an anesthetic agent) and memantine to prevent cognitive disorders following ECT41,42,69,70. In a study by Abbaszinari et al.20 on 40 major depressive disorder patients who received ECT treatment, the MMSE score at the end of the ECT session in the memantine group was significantly higher than the control group. In another study by Koola35, a combination of galantamine-memantine has also been shown to improve several cognitive domains in schizophrenia patients.

Herbs

Apart from using the above pharmacological agents, at least two studies published by Iranian researchers used herbs to prevent the cognitive adverse effects of ECT. Akuchekian et al.21 conducted a randomized double-blind clinical trial involving mood disorders in patients receiving ECT. The patients were either treated with a combination of Crocus sativus (CS), Cyperus rotundus (CR) and honey (n = 36), or placebo (n = 38) twice daily for 40 days from the first day of ECT. The authors found that CR, CS, and honey improved the memory side effects of ECT.

A similar clinical trial was conducted using Memoral herb. Thirty-three patients received Memoral herbal capsules (each containing 360 mg of Boswellia oleo-gum resin and 36 mg of Zingiber rhizome), and 30 patients received a placebo starting from the day before the first ECT. The MMSE score at the end of the ECT session in the memantine group showed significantly higher total Addenbrooke Cognitive Examination (ACE) scores compared to patients who received a placebo. However, both the authors did not put forward any possible mechanism of action of this herb in preventing ECT-induced cognitive impairment.

CONCLUSION

To date, there is no US Food and Drug Administration (FDA)-approved treatment for ECT-induced cognitive impairments. Based on our review, there are a few pharmacological agents/herbs found to confer beneficial effects in reducing cognitive impairment in humans.

REFERENCES


