Therapeutic and prophylactic role of cognitive enhancers in electroconvulsive therapy-induced cognitive deficits

ABSTRACT

Objectives: The objective is to evaluate the pattern of cognitive deficits after electroconvulsive therapy (ECT); to ascertain the role of various psychosocial, illness and treatment-related parameters on cognitive functions after ECT; and to evaluate the effect of donepezil on various cognitive deficits. Materials and Methods: A triple-blind randomized controlled trial was undertaken. Ninety patients undergoing ECT were included into study after due consent and institutional ethical approval. They were randomized into two groups: one using donepezil with ECT and the other using placebo with ECT. Various cognitive parameters were studied before ECT, after a course of ECT and after 4 weeks of last ECT. Findings were assessed in the light of available socialdemographic and clinical parameters and existing literature. Results: ECT was found to be an effective therapeutic modality. Immediate memory worsened over the course of ECT till after 4 weeks of ECT. Augmentation of donepezil was found useful. It sped up the improvement of general memory and working memory during ECT. Conclusion: Donepezil has therapeutic and prophylactic benefit on cognition of patients undergoing ECT over the course of treatment till 4 weeks after the ECT.

Keywords: Cognition, donepezil, electroconvulsive therapy, immediate memory

Convulsive therapy as a modality of treatment for major psychiatric illnesses had been reported to be in use since around fifteenth century.\(^1\,^2\) At present, electroconvulsive therapy (ECT) is widely used as effective therapy for a variety of psychiatric disorders including severe depression, acute psychosis, and suicidal patients.\(^3\) About 1 million patients with psychiatric disorders worldwide are treated with ECT annually.\(^3\,^4\) In recent years, a considerable...
A growing body of research has been consistently reporting adverse cognitive and psychological consequences of ECT among a substantial minority of patients. Cognitive impairments include memory and other aspects of cognition such as executive function, intelligence, reasoning, concentration, organizational skill, reasoning ability, and intelligence. Although discrepancies exist between clinician-led/hospital-based studies and those undertaken in collaboration with patients regarding the nature and extent of adverse side-effects; there is a general consensus that memory loss is the most frequent and consistently reported side-effect following ECT. Meta-analysis and systematic reviews have also differed in the categorization of side effects in terms of time after ECT as acute, subacute, and chronic with the period of manifestation of acute effects varying from initial 24 h in some reviews to 3 days after last ECT in others. Consensus regarding memory impairments following ECT lacks specificity; in addition, there is no consensus with regards to the subtypes of memory affected. Despite consistent reporting of adverse cognitive and psychological consequences of ECT among a substantial minority of patients, The true magnitude and duration of retrograde amnesia could not be estimated, as the person may never be completely aware of what he has forgotten. In view of variability in findings of cognitive deficits across studies, there is a need to assess the effect of ECT on cognition in our context; understand its extent and pattern, and consider any intervention which can decrease these cognitive deficits. This leads to the research question, Will addition of some medication decrease the post-ECT cognitive deficits? Few drugs have been tried in the past. Both animal and human studies showed some prospect in this dimension but finding mostly were variable and lacked replication. Drugs/group of drugs tried so far are N-methyl-D-aspartate receptor antagonists, cyclooxygenase inhibitors, calcium channel blockers, cholinesterase inhibitors, glucocorticoid receptor antagonists, nitric oxide donors, nootropic agents, opioids, vasopressin, adrenocorticotropic harmones, neuropeptides, ergoid mesylates, thyroid harmones, stimulants, and herbal preparations. Vasopressin was favored in early case reports but was not found effective in subsequent randomized controlled trials. Nimodipine did not differ significantly from placebo. Mentat and Memorin, herbal preparations, attenuated amnesic deficits in animal studies. Indomethacin held promise in attenuation of cognitive impairments following electro convulsive shocks in rats. Adrenocorticotropic hormone was found ineffective in immediate recall, memory retrieval, or consolidation of memory. A double-blind study on cytidine-5′-diphosphocholine-choline did not show any protection against ECT-induced memory dysfunction. Adjunctive T3 hormone showed better memory function in patient receiving ECT in a double-blind placebo controlled study. A double-blind intraindividual cross over comparison study of effect of piracetam on retrograde memory impairment following ECT did not replicate protective effects which was seen in animal studies. Piracetam had no significant effect in preventing ECT-induced memory disturbance in a randomized placebo controlled double-blind study. Galantamine was found protective against impairment in retention of new learning. It was safe and exhibited minimal adverse effects.

Few studies on donepezil made its use look more worthy for research in ECT-induced cognitive dysfunctions. In a triple-blind randomized controlled study; donepezil in low dosage was found to be significantly superior to placebo in improvement of immediate cognitive dysfunction. It was also found to be safe. Donepezil was successful in the treatment of cognitive impairment caused by maintenance ECT. Another study found donepezil to be effective in post ECT delirium and agitation. All these effects are explained by the hypothesis that post-ECT there is central nervous system cholinergic dysfunction which gets corrected by the use of cholinesterase inhibitor.

The present study was therefore undertaken to understand nature and pattern of cognitive deficits in patients post ECT, as well as any remedial role of donepezil in these cognitive deficits. This study is based on the evidence-based assumption that there are cognitive adverse effects due to ECT procedure. We aimed to study the therapeutic and prophylactic role of donepezil in ECT-induced cognitive deficits with objectives to evaluate the pattern of cognitive deficits after ECT; to ascertain the role of various psychosocial, illness, and treatment related parameters on cognitive functions after ECT; and to evaluate the effect of donepezil on various cognitive deficits after ECT.
ECT, coexistence of conditions which could interfere with cognitive testing (e.g., hearing impaired, impaired vision, and severe illness), or confound interpretation thereof (CNS diseases, concurrent medication known to interfere with cognitive testing), mental retardation, refusal to participate in study or patient with irregular follow-up were excluded from the study.

Self-made structured socio-demographic pro forma was administered to assess the demographic, family, clinical, social domains of participants along with data from collateral sources. Educational attainment of the subject was taken as proxy indicator of their cognitive reserve. Diagnoses of respective psychiatric illnesses were made using the ICD-10 criteria, becks depression inventory (BDI) and brief psychiatric rating scale (BPRS) were administered to measure severity of depression and psychosis respectively at baseline before ECT. Both the tests were given at baseline (2 days prior to giving ECT); after the course of ECT and after 4 weeks of ECT.

Wechsler Memory Scale III Indian adaptation (WMS III-Indian adaptation) was used to evaluate memory at baseline, after the course of ECT and after 4 weeks of ECT. Colored progressive matrices were used to assess the baseline intelligence.

Patients were evaluated clinically, were started on psychopharmacological treatment and the decision to administer ECT was purely taken on clinical indication for the same. Considering the aims and objectives of the study, only those cases that were given ECT were included in the study. Individuals were divided into two groups by computer-generated randomization. Patients in group “A” were subjected to 10 mg of donepezil hydrochloride tablet; which was started on the day the decision to administer ECT was taken; and discontinued after a week of ECT procedure. Patients in group ‘B’ were subjected to placebo of inert tablet; which was started on the day the decision to administer ECT was taken; and discontinued after a week of ECT procedure. Clinician administering ECT, staff recording data, and the statistical evaluator were blinded to the group (Triple blind). A special pro forma was also kept to record the side effects of medication; in both the groups.

All individuals received twice weekly, modified, bi-temporal ECT by brief pulse machine, starting 2 days after the baseline cognitive evaluations. The center of the electrode was positioned 1 inch (2.5 cm) above the midpoint of a line joining the external canthus of the eye with the external auditory meatus.

Details of seizure modification are as follows:

i. Atropine 0.6 mg intravenous (IV), immediately pre-ECT
ii. Succinylcholine, 0.5 mg/kg IV (subject to a maximum dose of 50 mg), immediately pre-ECT
iii. Thiopentone 2 mg/kg IV, immediately pre-ECT.

Care was taken to ensure good electrode-skin contact (using electrode jelly and firm pressure) with hand-held electrodes that are at least 3–4 cm in diameter. The patients were hyperventilated using pure, humidified oxygen for about 30–60 s pre-ECT and again, after ECT until spontaneous breathing recommenced. The entire anesthetic procedure was supervised by senior anesthetist and the ECT administration by a senior psychiatrist.

The ECT stimulus settings were as follows:

- Brief pulse/constant current-800 mA (milliAmperes)
- Pulse width-1.5 ms (milliseconds)
- Frequency-125 PPS (pulses per second)
- Duration-0.4–3.6 s corresponds to 60–540 mC (milli-Coulombs)

The starting dose of ECT for patients was 180 mC (milli-Coulombs). In case the patient did not experience adequate seizure, the dose was raised to the next level. An adequate seizure was defined as one that is at least 30 s long in motor duration. Seizures exceeding 120 s in duration were planned to be terminated using IV thiopentone/benzodiazepines as per availability. However, as recorded subsequently, all the cases had adequate seizure activity of the optimum duration. Post-ictal recovery was uneventful.

After the administration of six such ECTs and on recovery from the acute disorientation following last (6th) ECT, the WMS III-Indian adaption was administered. This was generally administered in the evenings of the day the patient received his last ECT (ECT was administered in the mornings). BDI and BPRS were administered after the course of six ECTs.

Patients were continued to be managed with medications based on their clinical condition and as per standard guidelines. All patients were sent on convalescent leave to consolidate the gains of therapy and re-admitted after 4 weeks. Wechsler Memory Scale III Indian adaptations, BDI, and BPRS were administered for the third time for each patient; on their rejoicing from leave. There was no loss of patients during follow-up and all 90 patients were available.

The Wechsler memory scales are individually administered,
components of a patient’s memory. The WMS-III Indian adaptation (WMS-III IN) is considered appropriate for use in Indian context. Average subtest internal consistency and reliability coefficients range from the 0.70s to the 0.90s. The average test-retest coefficient ranges from 0.56 to 0.80. The inter-scorer agreement reliability coefficients for the subtests requiring the most scoring judgments were all >0.90. It has the following components: immediate memory (further divided into auditory immediate memory and visual immediate memory), general memory (includes auditory delayed memory, visual delayed memory, and auditory recognition), and working memory.

The beck depression inventory is a 21-question multiple-choice self-report inventory for measuring the severity of depression. BDI contains 21 questions, each answer being scored on a scale value of 0–3. Higher total scores indicate more severe depressive symptoms. The test has high internal consistency of $\alpha = 0.91$. BPRS is a 16-item rating scale to measure positive symptoms, general psychopathology and affective symptoms. It has been used commonly in psychotic disorders. Each symptom is rated 1–7. The higher the score, more severe is the disorder. Measures on BPRS are stable over time and have good inter-rater reliability.

Colored progressive matrices are designed for the assessment of intelligence. The test contains sets A and B from the standard matrices, with a further set of 12 items inserted between the two, as set Ab. Most items are presented on a colored background to make the test visually stimulating for participants. This format is designed to measure reasoning ability and the eductive component of Spearman’s g.

Mini-mental status examination is a brief 30 point questionnaire test used as screening test for cognitive impairment. It takes about 10 min and examines functions such as arithmetic, memory, and orientation.

The resultant means and standard deviations of various parameters at the three points in time were compared using SPSS software—Version 20. This was done to assess whether the scores differed significantly over the three time points.

i. Scores after the course of six ECTs were compared with baseline in both the groups and between the two groups

ii. Scores 4 weeks after the last ECT were compared with the scores after the course of six ECTs in both the groups and between the groups

iii. Scores 4 weeks after the last ECT were compared with the scores at baseline in both the groups and between the groups

Results

During the study, 90 patients were given six ECTs, at the rate of two ECTs in a week. Tests were conducted for all patients before the ECT, after the six ECTs and 4 weeks after the last ECT. There was no loss of cases in the follow-up. Individuals, who were given donepezil, did not report any adverse event.

Sociodemographic and clinical parameters in the nondonepezil group and donepezil group are as shown in Table 1. There was no statistical difference between the group having ECT with donepezil and the one without; with respect to these parameters [Table 1]. Depression and psychosis significantly improved over the course of treatment in both nondonepezil group and donepezil group. There was no statistical difference between the two groups after 4 weeks of ECT as regards to improvement level and scores of measures of depression and psychosis. Effects on memory cognition across from baseline to 4 weeks of ECT in nondonepezil group and donepezil group are as shown in Tables 2 and 3, respectively. In nondonepezil group, immediate memory worsened significantly from the baseline over the course of ECT till after 4 weeks of ECT where as general memory and working memory improved significantly over the course. In the donepezil group, immediate memory statistically improved from the baseline to after the course of ECT but had statistical decline after that till after 4 weeks of ECT. Overall, however, there was no statistical difference from the baseline over the course of treatment till after 4 weeks of ECT. General memory and working memory improved significantly over the course in the donepezil group as well.

Effects of various variables on immediate memory after a course of ECT in both the groups are shown in Table 4. In nondonepezil group, there was significant association of scores of immediate memory after a course of ECT; with age, years of service, years of schooling, symptom duration, seizure duration, dose of ECT, working memory at baseline, and depression at baseline. There was no association with psychosis at baseline. In donepezil group, the same association was lost with symptom duration and working memory at baseline. Psychosis at baseline and intelligent quotient continued to have no association.

Effects of various variables on general memory after a course of ECT (both groups) are shown in Table 5. In nondonepezil group, there was significant association of scores of general memory after a course of ECT; with age, years of service, years of schooling, symptoms duration, seizure duration, dose of ECT, working memory at baseline, depression at baseline, and intelligence quotient. There was no association with psychosis at baseline. In donepezil group, the same association was lost with
symptom duration, dose of ECT, working memory at baseline, depression at baseline, and intelligence quotient. Psychosis at baseline continued to have no association.

**DISCUSSION**

Most of the individuals in the nondonepezil and donepezil groups had similar attributes. This enhanced the robustness of the research and the merit in the findings of research. There was no significant difference between the two groups at the baseline with respect to various sociodemographic and clinical parameters.

The analysis of treatment outcome, the primary goal of management; revealed that the scores of depression and psychosis improved over the course of treatment from the...
Immediate memory worsened significantly from the baseline over the course of ECT in the nondonepezil group. The worsening continued even after the course of ECT till after 4 weeks of ECT. This amply emphasizes various research findings that the ECT procedure does produce significant cognitive dysfunction.[13-15,16] However, in the same nondonepezil group, there was no worsening of general memory and the working memory. Rather both general and the working memory improved over the course of ECT from baseline to after the course of ECT and continuing till 4 weeks after the ECT. This finding is also no alien. Many a researchers have found that the memory scores did improve rather than reduce after ECT. Some attributed it to improvement in clinical parameters which improves the cognitive state as well.[19] Whether each facets of memory have significantly different neurobiological basis and are likely to get affected differently; rather contrastingly; is a worthy speculation but definitely not in the purview of the present research.

In donepezil group, it was observed that the immediate memory statistically improved from the baseline to after the course of ECT suggesting a protective action. However, after that, it had a statistical decline till after 4 weeks of ECT. Whether it is due to stoppage of donepezil after the course of ECT or due to any other reason; is a subject for further exploration. Overall, however, there was no statistical difference from the baseline over the course of treatment till after 4 weeks of ECT. Considering the ongoing worsening of immediate memory, till 4 weeks after the ECT, in the nondonepezil group; this trend suggests a neutralizing effect by donepezil. General memory and working memory improved similarly over the course in the treatment. Study suggests some beneficial action of donepezil on the cognitive effects of ECT, however, needs further replication with specific to various subtypes of memory. The various research in the past had shown promises of such nature.[35-37]

In nondonepezil group, immediate memory after a course of ECT was significantly associated with age, years of service, years of schooling, symptom duration, seizure duration, dose of ECT, working memory at baseline, and depression at baseline. With the addition of donepezil in other group, it was seen that the earlier observed association was lost with symptom duration, working memory at baseline, and processing speed at baseline. This suggest the capability of donepezil, when added; to neutralize the effect of symptom duration, working memory at baseline

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**Table 4: Effects on various variables on immediate memory after a course of electroconvulsive therapy (both groups)**

| Variables                  | ANOVA (F), P |  |  |
|----------------------------|--------------|  |  |
|                           | Nondonepezil | Donepezil |  |
| Age (years)               | 189.755      | 7.165     |  |
| Years of service          | 62.805       | 9.631     |  |
| Years of schooling        | 19.655       | 6.320     |  |
| Symptom duration (days)   | 62.365       | 0.692     |  |
| Seizure duration (s)      | 82.866       | 2.480     |  |
| Dose of ECT (milli-coulombs) | 29.952   | 6.010     |  |
| Working memory at baseline | 5.688      | 1.592     |  |
| Depression at baseline    | 11.879       | 2.847     |  |
| Psychosis at baseline     | 0.865        | 0.439     |  |
| Intelligence quotient     | 2.353        | 1.209     |  |

ECT – Electroconvulsive therapy; S – Significant; NS – Not significant

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**Table 5: Effects on various variables on general memory after a course of electroconvulsive therapy (both groups)**

| Variables                  | ANOVA (F), P |  |  |
|----------------------------|--------------|  |  |
|                           | Nondonepezil | Donepezil |  |
| Age (years)               | 8.4220       | 3.341     |  |
| Years of service          | 10.012       | 3.326     |  |
| Years of schooling        | 11.952       | 4.555     |  |
| Symptom duration (days)   | 15.941       | 0.626     |  |
| Seizure duration (s)      | 32.933       | 2.950     |  |
| Dose of ECT (milli-Coulombs) | 9.218    | 1.89     |  |
| Working memory at baseline | 11.958     | 0.681     |  |
| Depression at baseline    | 3.602        | 1.327     |  |
| Psychosis at baseline     | 0.865        | 0.111     |  |
| Intelligence quotient     | 2.469        | 0.898     |  |

ECT – Electroconvulsive therapy; S – Significant; NS – Not significant
or the processing speed on the immediate memory after the ECT treatment. As the use of cognitive enhancers and its utility in ECT is still in its infancy, no research exists in this direction. However, putative role of cholinergic pathway may definitely be conjectured and further be researched on to have more scientific management in future.

Similarly, in nondonepezil group, general memory after a course of ECT was significantly associated with age, years of service, years of schooling, symptoms duration, seizure duration, dose of ECT, working memory at baseline, depression at baseline and Intelligence Quotient. Symptom duration, dose of ECT, working memory at baseline, depression at baseline, processing speed at baseline, and intelligence quotient lost its impact in the group using donepezil with ECT. Findings are of pioneer nature and needs replication for further validation. The research suggests role of cholinergic pathway in such observation.

**CONCLUSION**

ECT is an effective therapeutic modality regardless of the controversies surrounding its use and the use of donepezil does not affect the outcome of the illness per se favorably or adversely. There was no worsening of general memory and the working memory. Rather both improved over the course of ECT and continuing till 4 weeks after the ECT. General memory and working memory improved in both the groups; with ECT. The addition of donepezil neutralized the observed association (in nondonepezil group) of immediate memory (after ECT treatment) with symptom duration, working memory at baseline, and processing speed at baseline. It also neutralized observed association of general memory (after ECT treatment) with symptom duration, dose of ECT, working memory at baseline, depression at baseline, processing speed at baseline, and intelligence quotient.

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**Conflicts of interest**

There are no conflicts of interest.

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