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Cognitive Protection after ECT: A Randomized Trial of Donepezil and Liothyronine in Mood Disorder Patients

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ABSTRACT

Background: Electroconvulsive therapy (ECT) is one of the most effective interventions available for severe or treatment-resistant mood disorders such as major depressive disorder (MDD) and bipolar depression, yet it is commonly accompanied by cognitive adverse effects that can hinder recovery and reduce quality of life. This trial was designed to assess whether donepezil, a cholinesterase inhibitor, and liothyronine, a synthetic thyroid hormone, could lessen the cognitive impairment that often follows ECT.

Methods: Sixty inpatients with mood disorders scheduled for ECT were allocated at random to one of three arms liothyronine 25 mcg/day, donepezil 5 mg/day, or donepezil 10 mg/day. Cognition was evaluated with the Addenbrooke's Cognitive Examination, Third Edition (ACE-III), before treatment began, 24 hours after the last ECT session, and again at one and two months afterward.

Results: Scores on the ACE-III rose over time in every arm across the attention, memory, fluency, and language domains, and none of the three groups differed significantly from one another at any assessment point indicating that donepezil and liothyronine conferred a similar degree of cognitive protection.

Conclusion: Both donepezil and liothyronine appear effective in reducing ECT-related cognitive impairment. Either agent may reasonably be considered as an adjunctive treatment to help preserve cognitive function in patients undergoing ECT.

Introduction

For decades, electroconvulsive therapy (ECT) has served as a mainstay treatment for severe mood disorders, including bipolar disorder and MDD, especially when symptoms are life threatening or unresponsive to medication. Despite its strong efficacy, ECT carries a risk of cognitive adverse effects that can slow recovery and diminish quality of life (1). These cognitive impairments can range from mild, transient memory lapses to persistent difficulties with attention, concentration, and executive functioning (2).

While most such effects resolve over time, a subset of patients experiences longer-lasting deficits that meaningfully interfere with daily functioning and delay rehabilitation. Retrograde and anterograde amnesia, cognitive slowing, and impaired memory and attention functions that depend on brain regions central to executive control are among the most commonly reported problems. The persistence of these deficits in some patients has fueled interest in adjunctive treatments capable of limiting cognitive side effects without compromising the therapeutic benefit of ECT.

Because the most effective pharmacological approach for preventing or treating these cognitive consequences remains unsettled, identifying candidate cognitive enhancers to pair with ECT has become an active area of research (3-5).

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Donepezil is an acetylcholinesterase inhibitor primarily prescribed for Alzheimer's disease; by raising cerebral acetylcholine levels, it may support memory, attention, and learning. Beyond dementia care, evidence indicates that donepezil can benefit cognition across a range of conditions marked by cognitive impairment (6). Given these apparent neuroprotective effects, it has been proposed as an adjunct to counter the cognitive side effects associated with ECT (7).

Liothyronine, the synthetic form of triiodothyronine (T3), has likewise drawn interest for its cognitive effects. Emerging evidence points to a role for thyroid hormones in improving cognition among depressed patients, particularly those with subclinical thyroid abnormalities, and liothyronine specifically has been linked to gains in memory and learning among hypothyroid patients making it a reasonable candidate for use alongside ECT given its favorable tolerability profile (8).

Although donepezil and liothyronine have each been studied individually, direct comparative evidence in patients undergoing ECT remains limited. This trial was therefore designed to close that gap, comparing the cognitive effects of donepezil and liothyronine in hospitalized mood-disorder patients receiving ECT. The primary objective was to determine which medication more effectively reduced cognitive impairment following ECT, while secondary objectives examined each drug's effect on specific cognitive domains and whether patient characteristics influenced treatment outcomes. Cognition was assessed using the Addenbrooke's Cognitive Examination (ACE-III).

Methods and Materials

This trial, using a double-blind, randomized design, took place at Shahid Yahya-nejad Hospital in Babol, Iran. Institutional ethics committee approval was obtained before the trial began, and every participant gave written informed consent prior to enrollment; the study followed applicable local ethical standards as well as the principles of the Declaration of Helsinki.

Sixty inpatients with a diagnosis of either MDD or bipolar depression (depressive phase) were enrolled; the mean number of ECT sessions was about 7.4, with no significant differences between groups. all were scheduled to undergo ECT as part of their treatment plan. Patients were eligible if they were (1) 18-65 years of age, (2) diagnosed with MDD or bipolar depression per DSM-5 criteria, and (3) clinically suitable candidates for ECT. Exclusion criteria included (1) comorbid neurological disorders (e.g., epilepsy, dementia), (2) serious medical conditions (e.g., cardiovascular disease), (3) current or past substance use disorder, and (4) pregnancy or breastfeeding. Random allocation placed participants into one of three arms: donepezil 5 mg/day, donepezil 10 mg/day, or liothyronine 25 mcg/day. Study medication began 24 hours before the first ECT session and continued for two months following the final session. Sessions of ECT were delivered three times weekly, with the total course ranging from six to nine treatments depending on clinical response. Dosages were chosen based on prior studies supporting the cognitive-enhancing potential of both donepezil and liothyronine in depressive populations.

The ACE-III, a five-domain instrument covering attention, memory, fluency, language, and visuospatial function, was used to evaluate cognitive status. Assessments occurred at four-time points baseline (before ECT), 24 hours after the final session, and one and two months later with the total ACE-III score serving as the primary outcome measure; subdomain scores across the five cognitive areas served as secondary outcomes.

Statistical analyses were performed in SPSS (version 25.0), while R was used to generate figures; baseline characteristics were summarized using descriptive statistics. Chi-square tests were applied to categorical variables, and a repeated-measures ANOVA examined between-group differences in ACE-III scores across time; statistical significance was set at $p<0.05$ throughout, with post hoc comparisons carried out as needed.

Results

Baseline characteristics are shown in Table 1; the three arms did not differ meaningfully in age, sex distribution, or number of ECT sessions received. Participants' overall mean age was 45.2 years, gender was fairly evenly split within each arm, and

Table 1. Baseline Characteristics of Participants

Characteristic	Donepezil 5 mg (n=20)	Donepezil 10 mg (n=20)	Liothyronine 25 mcg (n=20)
Age (mean ± SD)	45.2 ± 8.3	44.7 ± 7.9	45.0 ± 8.1
Gender (Male/Female)	10/10	11/9	12/8
ECT Sessions (mean)	7.4 ± 1.2	7.3 ± 1.1	7.5 ± 1.3

Cognitive performance, as measured by ACE-III scores, improved over time across all groups. Table 2 summarizes total ACE-III scores at 24 hours, 1 month, and 2 months after ECT. None of the three arms differed significantly from the others at any assessment point.

Table 2. ACE-III Scores at Different Time Points

Time Point	Donepezil 5 mg	Donepezil 10 mg	Liothyronine 25 mcg
24 hours post-ECT	78.5 ± 5.2	79.1 ± 4.8	78.9 ± 5.0
1-month post-ECT	82.3 ± 5.0	83.0 ± 4.7	82.7 ± 4.9
2 months post-ECT	85.0 ± 4.6	85.4 ± 4.4	85.1 ± 4.5

The repeated-measures ANOVA showed no significant between-group effect for total ACE-III scores, F (2,57) = 0.32, p=0.73, and this pattern held across every cognitive subdomain: attention, F (2,57) = 0.52, p=0.60; memory, F (2,57) = 0.42, p=0.66; fluency, F (2,57) = 0.45, p=0.64; and language, F (2,57) = 0.29, p=0.74. Together, these findings point to a comparable degree of cognitive benefit from donepezil and liothyronine after ECT. Figure 1 depicts the ACE-III score trajectories for the three treatment groups over time; all three arms show parallel gains from 24 hours to two months post-ECT, with no meaningful divergence between them, reinforcing the absence of significant between-group differences reported in Table 2.

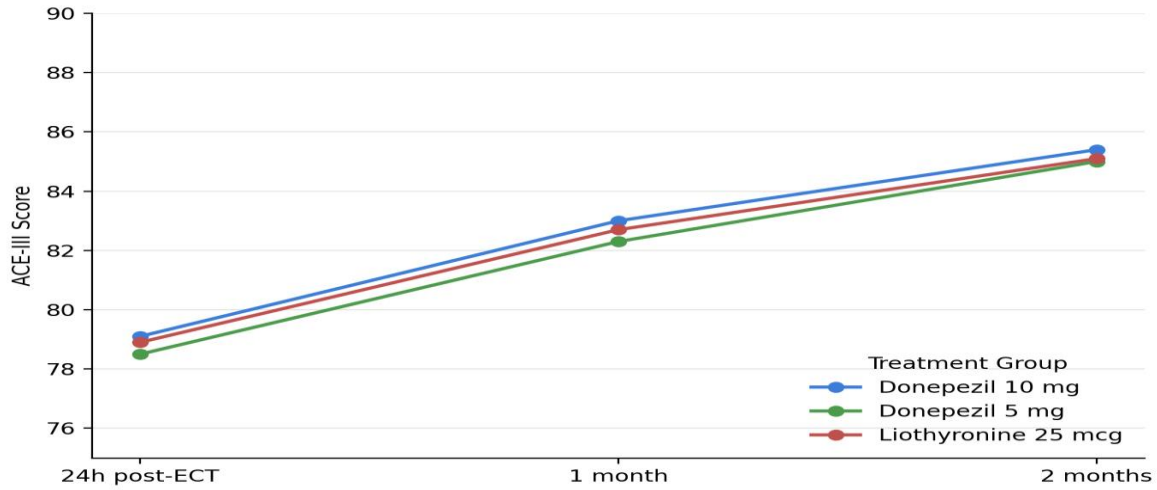

Figure 1. ACE-III scores over time by treatment group

Discussion

In this randomized trial, we examined how effectively donepezil (at 5 mg and 10 mg) and liothyronine (25 mcg) reduced cognitive impairment after ECT in patients with mood disorders. Across the two-month follow-up, every treatment arm showed meaningful gains on the ACE-III in attention, memory, fluency, language, and visuospatial performance. None of the three treatment arms differed significantly from one another, indicating a broadly equivalent degree of cognitive protection from donepezil and liothyronine after ECT. This is consistent with earlier work highlighting donepezil's capacity to enhance cognition in Alzheimer's disease and other conditions involving cognitive decline (9-11). Salloway and colleagues, for instance, documented notable gains in memory and attention among Alzheimer's patients treated with donepezil, lending support to a possible neuroprotective role for the drug in non-demented individuals undergoing ECT (9). The lack of a dose-dependent effect between the 5 mg and 10 mg donepezil arms fits with prior work suggesting that lower doses may already be sufficient to yield cognitive benefit in non-demented populations (10). Likewise, the improvements seen with liothyronine align with evidence tying thyroid hormones to better memory and learning in patients with depression or subclinical hypothyroidism (12). Bunevicius and colleagues, for example, found that liothyronine improved cognitive performance among depressed patients with thyroid dysfunction, pointing to a mechanism that could plausibly extend to ECT-related cognitive deficits (12).

Although this trial did not detect between-group differences, other work on donepezil has reported domain-specific gains, particularly in memory (11). Such discrepancies could stem from differences in the populations studied, ECT protocols, dosing schedules, or the cognitive instruments used a point also raised in a recent meta-analysis by Vasavada and colleagues (13). These results nonetheless carry meaningful clinical relevance: both donepezil and liothyronine emerge as reasonable adjuncts for preserving cognitive function during ECT, which could in turn improve tolerability and quality of life for patients (13). Given their relatively favorable side-effect profiles, both agents could plausibly be

incorporated into routine practice, particularly for patients at elevated risk of cognitive impairment, such as those with pre-existing cognitive deficits or longer ECT courses (14). At the same time, clinicians should weigh these benefits against possible risks gastrointestinal effects with donepezil, or thyroid-related effects with liothyronine and take patient-specific factors such as baseline thyroid function into account (15).

While mechanistic investigation was not a primary aim of this study, the cognitive benefits observed with both agents likely reflect their distinct neurochemical modes of action. Donepezil enhances cholinergic neurotransmission by inhibiting acetylcholinesterase, thereby increasing acetylcholine availability in brain regions critical for memory and attention. Liothyronine, by contrast, modulates gene expression and synaptic plasticity through thyroid hormone receptors, potentially improving cognition via metabolic and neurotrophic pathways. These distinct mechanisms offer a plausible biological rationale for using either agent to manage ECT-related cognitive impairment.

A number of limitations warrant mention. With only 60 participants, the study may have lacked sufficient statistical power to detect subtle between-group differences, particularly within specific cognitive domains. The fixed dosing used here may also not have captured potential dose-response relationships, particularly for donepezil, where higher doses might benefit some patients further (16-17). Because the trial was conducted at a single center, the findings may not generalize well to other clinical settings or to populations differing in demographic or clinical makeup (18-19). Future research should address these constraints through larger, multi-center trials that include a placebo arm to clarify the independent contribution of donepezil and liothyronine to cognitive protection. Exploring dose escalation or individualized dosing strategies could further refine treatment outcomes, particularly given the underexplored dose-response relationship for donepezil in ECT populations. Longer-term follow-up is also needed to determine whether these interventions affect sustained cognitive recovery or functional outcomes such as return to work or social functioning. Examining patient-specific factors baseline thyroid status or depressive symptom severity, for example may help identify which subgroups stand to benefit most, consistent with the broader move toward personalized psychiatric care.

Conclusion

In this randomized clinical trial, both donepezil and liothyronine were associated with improvements in cognitive performance following ECT in patients with mood disorders. That said, neither treatment showed a statistical advantage over the other in mitigating ECT-related cognitive effects, which points to the value of tailoring adjunctive cognitive-support decisions to the individual patient. The absence of a placebo arm and the modest sample size nonetheless highlight the need for larger, placebo-controlled studies to confirm these findings and to identify optimal dosing strategies.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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