Research Paper

Melatonin as a Neuroprotective Adjunct in Bipolar Patients Undergoing Electroconvulsive Therapy: A Double-blind Randomized Controlled Trial

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ABSTRACT

Introduction: Bipolar disorder (BD) is frequently treated with electroconvulsive therapy (ECT), which, despite its efficacy in severe mood episodes, is often complicated by cognitive impairment. To our knowledge, no standard prophylactic therapy currently exists to prevent these adverse effects. Melatonin, with established antioxidant and neuroprotective properties, may attenuate ECT-related cognitive dysfunction.

Methods: In this randomized, double-blind, placebo-controlled trial, 46 inpatients with BD undergoing ECT were allocated 1:1 to receive either melatonin (3 mg nightly) or identical placebo capsules. Study medication was administered from 24 h before the first ECT session until 24 h after the final session. Cognitive outcomes were assessed using the mini-mental state examination (MMSE) and its subdomains at baseline and after each ECT session. Secondary outcomes included systolic and diastolic blood pressure. Adverse events were recorded throughout the trial.

Results: Compared with placebo, melatonin significantly improved global cognition across the ECT course (group × time interaction, P=0.021). At the final session, patients receiving melatonin demonstrated higher MMSE scores (27.9±1.8 vs 26.5±2.0), with the strongest improvements in recall (+0.6 points, P=0.012) and attention/calculation (+0.5 points, P=0.018). Blood pressure (BP) values remained stable (Δ systolic BP: –1.2±3.1 mm Hg melatonin vs –0.8±2.9 mm Hg placebo, P=0.64), and melatonin was also well tolerated.

Conclusion: Adjunctive melatonin reduced ECT-related cognitive impairment in BD patients, with pronounced benefits in memory and attention, while maintaining an excellent safety profile. These findings support melatonin as a simple, inexpensive, and widely accessible therapeutic option to support cognition in this vulnerable population.

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Highlights

- Melatonin improved overall cognition in bipolar patients receiving ECT.
- The greatest cognitive gains were observed in the recall and attention/calculation domains.
- Melatonin was well tolerated with no significant adverse effects observed.
- No hemodynamic instability occurred during ECT sessions with melatonin use.
- Melatonin is a safe adjunctive option for reducing ECT-related cognitive decline.

Plain Language Summary

Electroconvulsive therapy (ECT) is a powerful and often life-saving treatment for people with severe bipolar disorder, especially when other treatments do not work. However, one of the biggest problems with ECT is that it can cause memory problems and difficulties with thinking, which makes many patients and families worried about choosing this treatment. Melatonin is a natural hormone produced by the body, best known for regulating sleep. But research has also shown that melatonin has protective effects on the brain, including reducing stress from harmful molecules (oxidative stress) and helping nerve cells work better. Because of these properties, we wanted to test whether melatonin could help protect patients from memory and thinking problems caused by ECT. In our study, 46 patients with bipolar disorder who were scheduled to receive ECT took part. Half of them received melatonin, and the other half received a placebo (an inactive pill) during their treatment course. We measured their thinking and memory using a standard test before and after ECT. Patients who took melatonin showed better performance, especially in remembering words and focusing on tasks, compared with those who took a placebo. Importantly, melatonin was safe and caused no serious side effects. These findings suggest that melatonin, which is inexpensive and widely available, could be a simple way to make ECT safer and easier for patients by protecting their memory. If confirmed in larger studies, this approach could encourage more patients to accept ECT when needed, thereby improving treatment outcomes and quality of life.

Introduction

Bipolar disorder (BD) is a severe, chronic mood illness affecting a vast population worldwide. Global burden estimates exceed 40 million affected individuals (Jiang et al., 2025; Millett et al., 2025), and BD ranks among the leading causes of disability. Importantly, cognitive deficits in attention, memory, and executive function are an essential and persistent feature of BD, present in roughly 40-60% of patients (Burdick et al., 2014; Millett et al., 2025). These impairments endure even during euthymic periods and strongly predict poorer psychosocial function and reduced quality of life (Nicoloro-SantaBarbara et al., 2023). Electroconvulsive therapy (ECT) is one of the most effective treatments for severe, treatment-resistant mood episodes, including bipolar depression and mania (Fetahovic et al., 2025). However, its utility is tempered by adverse cognitive sequelae: ECT commonly induces retrograde and anterograde memory impairment. For example, guidelines note that ECT frequently causes loss of autobiographical memory and short-term learning deficits (Porter et al., 2020), and up to ~60% of patients report new memory problems in the weeks following treatment (Porter et al., 2020). These cognitive side effects can substantially worsen overall functioning and diminish the therapy's quality-of-life benefits.

The mechanisms underlying ECT-induced cognitive dysfunction are not fully understood but are believed to be multifactorial. ECT-triggered seizures appear to provoke acute neurobiological stress. Recent work suggests that ECT increases mitochondrial activity and generates a surge of reactive oxygen species (ROS), along with transient elevations in pro-inflammatory cytokines (Freire et al., 2017). At the same time, ECT alters neurotransmitter systems (including glutamate, Gamma-aminobutyric acid (GABA), and monoamines) and neurotrophic signaling in cortico-limbic circuits (Fetahovic et al., 2025; Van Den Bossche et al., 2019). Together, these changes may transiently disrupt neuronal homeo-

stasis and plasticity, contributing to memory lapses. In response, researchers have trialed various pharmacologic adjuncts to blunt these effects. For instance, the N-methyl-D-aspartate (NMDA) antagonist memantine and thyroid hormone (liothyronine, T3) have shown some promise in limited trials (Verdijk et al., 2022). Small studies also tested acetylcholinesterase inhibitors (e.g. donepezil), with one review noting improved cognitive scores in most trials (Verdijk et al., 2022). Nevertheless, systematic reviews underscore that the evidence is weak and inconsistent: published trials vary widely in design and quality, and many findings remain contradictory or of low certainty (Freire et al., 2017; Verdijk et al., 2022).

Melatonin is an endogenous indoleamine hormone best known for regulating circadian rhythms, but it also has potent antioxidant and neuroprotective actions. Its lipophilic structure allows it to cross the blood–brain barrier and directly scavenge a broad spectrum of free radicals (Carretero et al., 2023; Kołodziejska et al., 2025). Melatonin elevates endogenous antioxidant defenses and inhibits pro-oxidant enzymes (Kołodziejska et al., 2025). It also exerts anti-inflammatory effects by suppressing microglial activation and the NF-κB pathway, thereby reducing the release of inflammatory cytokines (Sivamaruthi et al., 2023) including neurodegenerative illnesses like Alzheimer's disease (AD). These properties suggest that melatonin could protect against oxidative and inflammatory brain injury induced by ECT seizures. Empirical evidence for melatonin's cognitive benefits is mixed. In some studies, adjunctive melatonin improved subjective memory or cognitive scores: for example, depressed patients taking melatonin with antidepressants reported less perceived cognitive dysfunction (Colwell et al., 2022; Targum et al., 2015). Conversely, in one randomized controlled trial (RCT) of depressed patients undergoing ECT, low-dose melatonin (3 mg/d) was less effective than memantine at preventing post-ECT cognitive decline (Sarraf et al., 2020). In another trial (among hemodialysis patients), melatonin showed no significant benefit over placebo on cognition (Hatamkhani et al., 2024). On the other hand, studies in other contexts hint at neuroprotective effects. For instance, melatonin reduces cognitive deterioration in Alzheimer and Parkinson disease models (Talbot et al., 2023), and animal experiments demonstrate that melatonin can preserve hippocampal neuronal integrity and memory after brain injury (Chang et al., 2021).

Despite its promise, no standard prophylactic treatment for ECT-related cognitive impairment exists. Prior studies have been inadequate due to small sample sizes and heterogeneity in ECT techniques, drug dosing, and cognitive assessments (Verdijk et al., 2022). Thus, a clear gap remains. In other words, rigorous, placebo-controlled trials of melatonin in the ECT context are scarce. The present study aims to fill this gap by systematically evaluating whether adjunctive melatonin can mitigate cognitive side effects of ECT in bipolar patients. We hypothesize that patients receiving melatonin will demonstrate better cognitive performance after ECT (less memory and executive impairment) than those receiving a placebo.

Materials and Methods

Study design and setting

This study was a randomized, double-blind, placebo-controlled clinical trial conducted to assess the potential protective effects of melatonin on cognitive impairments associated with ECT in patients with BD. The trial was performed at Shafa Hospital, Rasht, Iran, a tertiary psychiatric referral center, between June 2023 and June 2024. Patients with a confirmed diagnosis of BD who were scheduled to undergo ECT were consecutively recruited and randomized to either the melatonin or placebo group.

The protocol was reviewed and approved by the Research Ethics Committee of Guilan University of Medical Sciences. The trial was prospectively registered in the Iranian Registry of Clinical Trials (IRCT). Written informed consent was obtained from all patients or their legal guardians before enrollment, following a detailed explanation of the study's objectives, procedures, potential benefits, and risks. All study procedures adhered to the ethical standards of the institutional review board and the principles of the Declaration of Helsinki.

Study participants

Adult patients aged 18 years or older with a clinician-confirmed diagnosis of BD according to the updated DSM5TR criteria (American Psychiatric Association, 2022) were eligible if they were scheduled to undergo an acute course of ECT at Shafa Hospital, Rasht City, Iran (American Psychiatric Association, 2022; First et al., 2022). The exclusion criteria comprised comorbid neurological disorders (e.g. epilepsy or dementia), severe systemic medical conditions such as significant hepatic, renal, or cardiac dysfunction, active gastrointestinal ulceration, uncontrolled hypertension, ongoing substance (alcohol or illicit drug) use, known hypersensitivity to melatonin, pregnancy or breastfeeding, concurrent use of medications with pronounced cognitive or sedative effects (e.g. high-dose benzodiazepines or anticholiner-

gic agents), and sensory or language impairments that precluded completion of neurocognitive assessments. All eligible participants or their legal guardians provided written informed consent before enrollment, after receiving comprehensive explanations of the study objectives, procedures, potential risks, and anticipated benefits. Participants were recruited consecutively during routine clinical evaluation and screened according to the predefined eligibility criteria. A history of prior ECT was not considered an exclusion criterion in this study.

Screening and enrollment

Potential participants were identified consecutively from patients referred for ECT and were initially evaluated by the attending psychiatrists in collaboration with a study pharmacist. The diagnostic process involved a structured clinical interview to confirm BD according to DSM-5-TR criteria, along with a comprehensive review of past medical history and current medications. A complete physical examination, including vital sign measurements, was performed to ensure clinical stability. Baseline safety assessments included a standard 12-lead electrocardiogram to rule out conduction abnormalities, particularly bradyarrhythmia, as well as routine laboratory investigations of renal and hepatic function. Women of childbearing potential underwent a pregnancy test before randomization, and toxicology screening was conducted when clinically indicated to exclude active alcohol or illicit drug use. Final eligibility was verified and recorded prospectively in study source documents and case report forms. Informed consent was obtained from all participants or their legal guardians before enrollment in the trial, in accordance with institutional guidelines and internationally accepted recommendations for ethical conduct in clinical trials and the use of ECT (First et al., 2022).

Randomization and blinding

Participants who met eligibility criteria were randomized in a 1:1 ratio to receive either melatonin or a placebo, in addition to standard ECT. The randomization sequence was generated using a computer-based system with permuted blocks of 4, implemented via a validated external randomization platform (Kim & Shin, 2014). Allocation concealment was ensured through sequentially numbered, opaque, sealed envelopes (SNOSE), prepared by a research coordinator who was not involved in patient recruitment, administration, or outcome assessments. Each envelope was opaque, tamper-proof, and stored centrally in the pharmacy, only opened upon formal patient enrollment—this approach effectively prevents selection bias (Clark et al., 2021).

The study was designed as a double-blind trial: neither the patients, the treating psychiatrists administering ECT, nor the cognitive evaluators were aware of the treatment allocations. Melatonin and placebo capsules were identical in appearance, packaging, and labeling to maintain blinding integrity. Data analysts remained blinded to group identities (coded as group A/group B) until the database was locked and the pre-specified statistical plan completed, in accordance with CONSORT guidelines for reporting blinding and intervention similarity (Hopewell et al., 2025).

Following participant consent, the study nurse retrieved the next envelope from the pharmacy, linked it to the corresponding medication kit, and administered the first dose per protocol, without involvement in eligibility determination or outcome assessments. Emergency unblinding was possible only with the pharmacy director's formal documentation; notably, no such events occurred. This protocol clearly distinguishes between allocation concealment and blinding and safeguards against both selection and performance biases (Vorland et al., 2021).

The sample size was calculated a priori based on conventional statistical standards. Using a two-tailed test with $\alpha=0.05$ and power of 80%, and assuming a medium effect size (Cohen's $d\approx0.5$), an estimated 34 participants per arm would be required to detect a clinically meaningful difference in cognitive outcomes (Hartman et al., 2017). To account for possible attrition (~10%–15%), the target enrollment was increased, resulting in 46 participants randomized and followed to study completion. The calculation followed the standard formula (Equation 1) for comparing two independent means in superiority trials:

$$1.\ \frac{((Z(1-\alpha/2)+Z(1-\beta))^2\times(\sigma^2+\sigma_2^2))}{\Delta^2}=\text{n per group}$$

, where σ and σ2 are group standard deviations, Δ is the expected mean difference, and Z denotes standard normal quantiles (Serdar et al., 2021). Figure 1 shows patient screening, randomization, allocation, follow-up, and analysis.

Intervention protocol

Participants randomized to the intervention arm received oral melatonin 3 mg capsules (Tehran Darou Pharmaceutical Co., Tehran, Iran) once nightly at 21:00±30 minutes to synchronize with the endogenous circadian rhythm of melatonin secretion. The first dose was administered 24 hours before the initiation of the ECT course, and treatment continued daily until 24 hours after the fi-

nal ECT session, yielding an average exposure duration of approximately two weeks. Capsules were dispensed in sealed, coded blister packs by the hospital pharmacy, with identical-appearing placebo capsules produced by the same company to ensure indistinguishability. Matching was confirmed for capsule size, shape, color, taste, odor, and packaging to maintain blinding integrity. Adherence was reinforced through directly observed therapy: all doses were administered under the supervision of trained ward nurses, who documented administration times in case report forms. Missed doses, if any, were recorded along with reasons, and participants were not allowed to self-administer medication. To safeguard trial integrity, returned packs were counted to verify compliance. The control group received placebo capsules under identical procedures. Both melatonin and placebo were stored at controlled room temperature (20–25 ˚C) and monitored for stability throughout the study. The double-blind design extended to all treating clinicians, outcome assessors, and data analysts.

ECT procedures were standardized across both arms. Treatments were delivered using a Thymatron® System IV device (Somatics LLC, Lake Bluff, IL, USA) with brief-pulse, constant-current stimulation and bilateral electrode placement. Stimulation parameters were individualized using the half-age method to estimate the seizure threshold and minimize cognitive adverse effects. Each session was titrated to achieve a motor seizure lasting at least 25 s and an EEG-confirmed seizure lasting ≥30 s, with adequacy determined by cuff-isolated limb observation and EEG monitoring. Patients typically underwent six ECT sessions over the treatment course, consistent with standard psychiatric practice and contemporary international ECT guidelines (American Psychiatric Association, 2022; Choe et al., 2020).

Outcome measures

The primary outcome was the change in global cognitive performance, assessed by the MMSE, measured repeatedly at baseline (within 24 hours before the first ECT session) and 24 hours after each ECT session, including the sixth (final) session. The MMSE, a standardized 30-point screening instrument evaluating domains such as orientation, attention, memory, language, and visuospatial ability, is well-established in clinical research. For this study, the validated Persian version of the MMSE, with demonstrated high internal consistency (Cronbach α=0.81) and construct validity in Iranian populations, was administered by a trained research assistant blinded to treatment assignment (Khodamoradi et al., 2020).

Secondary outcomes included changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP), measured at the same timepoints as the cognitive assessments. BP monitoring was incorporated as a secondary safety parameter to evaluate possible hemodynamic effects of melatonin during the ECT course, given its known influence on circadian regulation and vascular tone. BP was recorded after participants rested for at least 5 minutes, using a calibrated automated digital sphygmomanometer (Beurer BM28; Beurer GmbH, Ulm, Germany). The measurement protocol adhered strictly to the American Heart Association (AHA) recommendations for accurate and standardized BP assessment, which emphasize a rest period, a correctly sized cuff, and proper body positioning (Asmar et al., 2024; Muntner et al., 2019). All BP measurements were performed by experienced, blinded staff, and the measurement devices were calibrated weekly to ensure precision and reproducibility.

Statistical analysis

Data were analyzed using SPSS software, version 26 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as Mean±SD, and categorical variables are reported as frequencies and percentages. Baseline characteristics were compared with independent samples t-tests or chi-square tests, as appropriate. Changes in total MMSE across ECT sessions were examined using linear mixed-effects models that included group, time, and their interaction. Paired t-tests assessed within-group changes from baseline, and Welch's t-tests were used for between-group comparisons at each session. The Holm-Bonferroni method was applied to control for multiple comparisons. Subdomain-level MMSE scores were analyzed by paired t-tests for within-group changes (baseline vs ECT6) and by Welch's t-tests for between-group differences at ECT6 and for difference-in-change values (ΔMel − ΔPlac). Results were summarized in tables and illustrated with forest plots. For secondary physiological outcomes (SBP and DBP), pre–post changes were evaluated with paired t-tests, and between-group differences in change scores with independent-samples t-tests. Findings were visualized with line plots (mean±95% CI) and bar plots of Δ-values.

Results

Baseline characteristics

A total of 46 participants were randomized: 23 to melatonin and 23 to placebo. Demographic and physiological characteristics were well balanced across treatment

arms. The average age of participants was comparable between groups, and sex distribution did not differ significantly.

At baseline, both groups demonstrated similar MMSE scores. Orientation to time and place, registration, and most language domains were near ceiling levels, whereas the greatest variability was observed in recall and attention/calculation tasks. These patterns are consistent with prior reports of subtle baseline cognitive deficits in patients with BD undergoing ECT. The mean total MMSE score was 26.6±1.9 in the melatonin group and 26.2±2.0 in the placebo group, with no statistically significant difference. Physiological measures, including systolic and diastolic BP, were also comparable between groups at baseline. Detailed baseline characteristics are summarized in Table 1.

Primary outcome

Change in total MMSE score across ECT sessions

Across the trial, between-group comparisons demonstrated a consistent but nonsignificant trend favoring melatonin over placebo at all time points (Table 2). Linear mixed-effects analysis further confirmed significant main effects of time ($F_{5, 210}$=11.27, P<0.001) and a significant group × time interaction ($F_{5, 210}$=2.98, P=0.021), indicating that melatonin-treated patients showed greater cognitive improvement across ECT sessions than placebo-treated patients (Supplementary Table 1). However, within-group analyses provided clearer insights. In the melatonin arm, patients showed progressive improvement in global cognitive performance relative to baseline. Significant gains emerged at the third ECT session, where MMSE scores increased by an average of 0.7 points (95% CI, 0.08%, 1.32%; P<0.05). This improvement was sustained, with further enhancement observed

Table 1. Baseline demographic, cognitive, and physiological characteristics of participants

Variables		Mean±SD/No. (%)		P
		Melatonin (n=23)	Placebo (n=23)	
Demographics	Age (y)	38.6±7.4	38.5±7.1	0.982
	Female sex	12(52.2)	7(30.4)	0.769
Cognitive performance (MMSE subdomains)	Orientation to time (0–5)	4.6±0.6	4.5±0.7	0.613
	Orientation to place (0–5)	4.7±0.5	4.6±0.6	0.552
	Registration (0–3)	3±0	3±0	1.000
	Attention & calculation (0–5)	3.6±0.9	3.5±0.9	0.684
	Recall (0–3)	1.6±0.8	1.5±0.8	0.731
	Naming (0–2)	2±0	2±0	1.000
	Repetition (0–1)	1±0	1±0	1.000
	3-stage Command (0–3)	3±0	3±0	1.000
	Reading (0–1)	1±0	1±0	1.000
	Writing (0–1)	1±0.1	1±0.1	0.818
	Visuospatial (0–1)	1±0	1±0	1.000
	Total MMSE (0–30)	26.6±1.9	26.2±2	0.441
Physiological variables	Systolic BP (mm Hg)	126±12	125±11	0.772
	Diastolic BP (mm Hg)	78±8	77±7	0.813

Abbreviations: MMSE: Mini-mental state examination; BP: Blood pressure; SD: Standard deviation.

Table 2. Between-group comparison of MMSE scores across ECT sessions

Session	Mean		Mean Difference	95% CI		$F_{1, 44}$	P	Sig.
	Melatonin	Placebo		Low	High			
Baseline	26.6	26.2	0.4	-0.4	1.2	1.02	0.321	
ECT1	26.5	25.9	0.6	-0.19	1.39	2.37	0.131	
ECT2	27	25.8	1.2	0.42	1.98	9.46	0.003	**
ECT3	27.3	26	1.3	0.5	2.1	10.26	0.002	**
ECT4	27.16	26.3	0.86	0.06	1.66	4.65	0.037	*
ECT5	27.48	26.6	0.88	0.09	1.68	4.98	0.030	*
ECT6	27.9	26.5	1.4	0.75	2.05	14.87	<0.001	***

*P<0.05, **P<0.01, ***P<0.001.

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by the fifth session (mean change 0.88; 95% CI, 0.17%, 1.60%; P<0.05). The largest improvement occurred at the final ECT session, where scores rose by 1.3 points relative to baseline (95% CI, 0.59%, 2.01%; P<0.01), indicating a cumulative neuroprotective effect (Table 3). In contrast, participants in the placebo arm showed no significant change in MMSE performance throughout the ECT course. Although minor fluctuations were observed, none reached statistical significance compared to baseline (Table 3).

Subdomain-level changes in MMSE

Subdomain analyses provided more granular insights into the cognitive effects of melatonin compared with placebo. Between-group comparisons at the final ECT

Table 3. Within-group changes in MMSE

Session		Mean Change vs Baseline	P		95% CI		Sig.
			Raw	Holm	Low	High	
Melatonin arm	ECT1	-0.1	0.77	0.77	-0.8	0.6	
	ECT2	0.4	0.277	0.555	-0.35	1.15	
	ECT3	0.7	0.029	0.117	0.08	1.32	
	ECT4	0.56	0.147	0.441	-0.21	1.33	
	ECT5	0.88	0.018	0.088	0.17	1.6	
	ECT6	1.3	0.001	0.006	0.59	2.01	**
Placebo arm	ECT1	-0.3	0.518	1	-1.25	0.65	
	ECT2	-0.4	0.462	1	-1.51	0.71	
	ECT3	-0.2	0.701	1	-1.27	0.87	
	ECT4	0.1	0.836	0.836	-0.89	1.09	
	ECT5	0.4	0.421	1	-0.61	1.41	
	ECT6	0.3	0.503	1	-0.61	1.21	

ECT: Electroconvulsive therapy.

**P<0.01.

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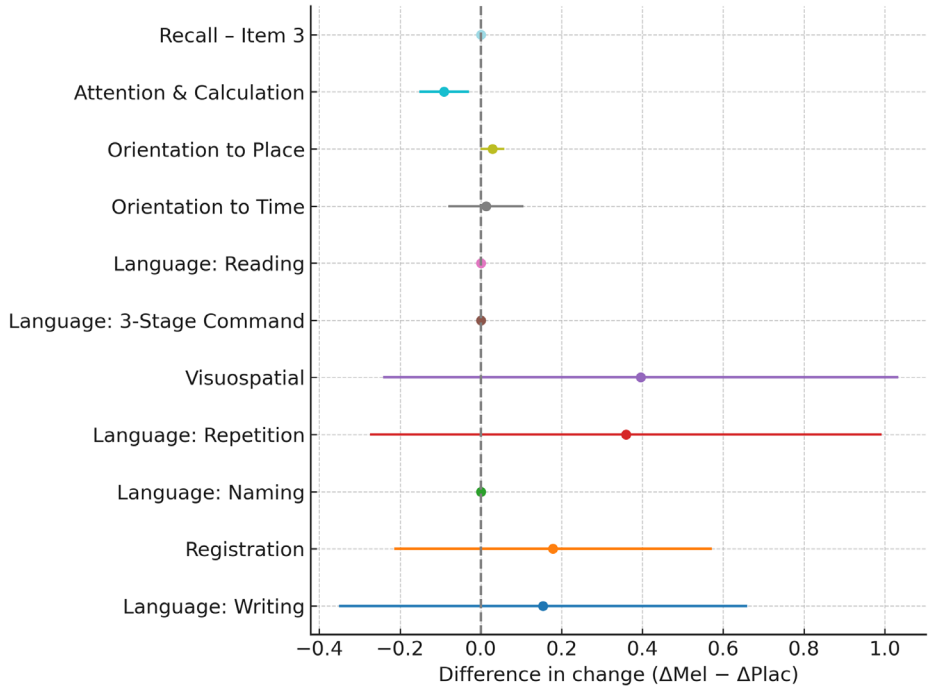

Figure 1. CONSORT flow diagram of the trial

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Note: The flow diagram illustrates patients' screening, randomization, allocation, follow-up, and analysis. A total of 90 patients were assessed for eligibility; 23 were excluded (17 with schizophrenia and 6 for other reasons). Sixty-seven patients were randomized to receive either melatonin (n=36) or a placebo (n=31). After dropouts (13 and 8, respectively), 23 participants in each group completed the study and were included in the final analysis.

session (ECT6) revealed that the largest numerical advantages for melatonin were observed in the recall and attention & calculation domains, with mean differences of approximately +0.5 and +0.4 points, respectively, relative to placebo (Figure 2A). Smaller favorable shifts were also noted in orientation to place and orientation to time. In contrast, language-related subdomains (naming, repetition, reading, and writing) and visuospatial ability remained essentially unchanged across groups. Conversely, a modest negative difference in Writing was observed at ECT6 (mean difference ≈−0.08), reflecting minor decrements in both groups but more pronounced in the melatonin arm (Figure 2A).

When changes from baseline to ECT6 were compared directly between groups (ΔMel − ΔPlac), the superiority of melatonin became more apparent (Figure 2B). Participants receiving melatonin exhibited significant within-group improvements in Recall (+0.7 points) and attention & calculation (+0.6 points). In contrast, placebo recipients showed only small, nonsignificant gains (+0.3 and +0.2, respectively). The difference-in-change analysis confirmed that melatonin exerted a stronger protective effect in memory and attentional domains, consistent with its hypothesized neuroprotective and antioxidant mechanisms. By contrast, orientation and procedural command subdomains demonstrated negligible or mixed changes, and language-related functions remained at ceiling performance in both groups, thereby limiting sensitivity to detect between-group differences.

Secondary outcomes (blood pressure)

No significant differences were observed between groups in BP outcomes. Mean SBP values remained stable across the trial, with a small nonsignificant decrease in the melatonin arm (−1.4 mm Hg) and a slight increase in the placebo arm (+0.8 mm Hg; between-group P=0.29). Similarly, DBP showed minimal within-group fluctuations (−0.7 mm Hg in the melatonin group vs +0.5 mm Hg in the placebo group), with no significant between-group difference at study end (P=0.34) (Figure 3).

Safety and tolerability

Melatonin was generally well tolerated. No serious adverse events were observed in either group. Mild and transient side effects were reported, including headache in 2 patients (1 melatonin, 1 placebo) and daytime sleepiness in 3 patients (2 melatonin, 1 placebo). None of these

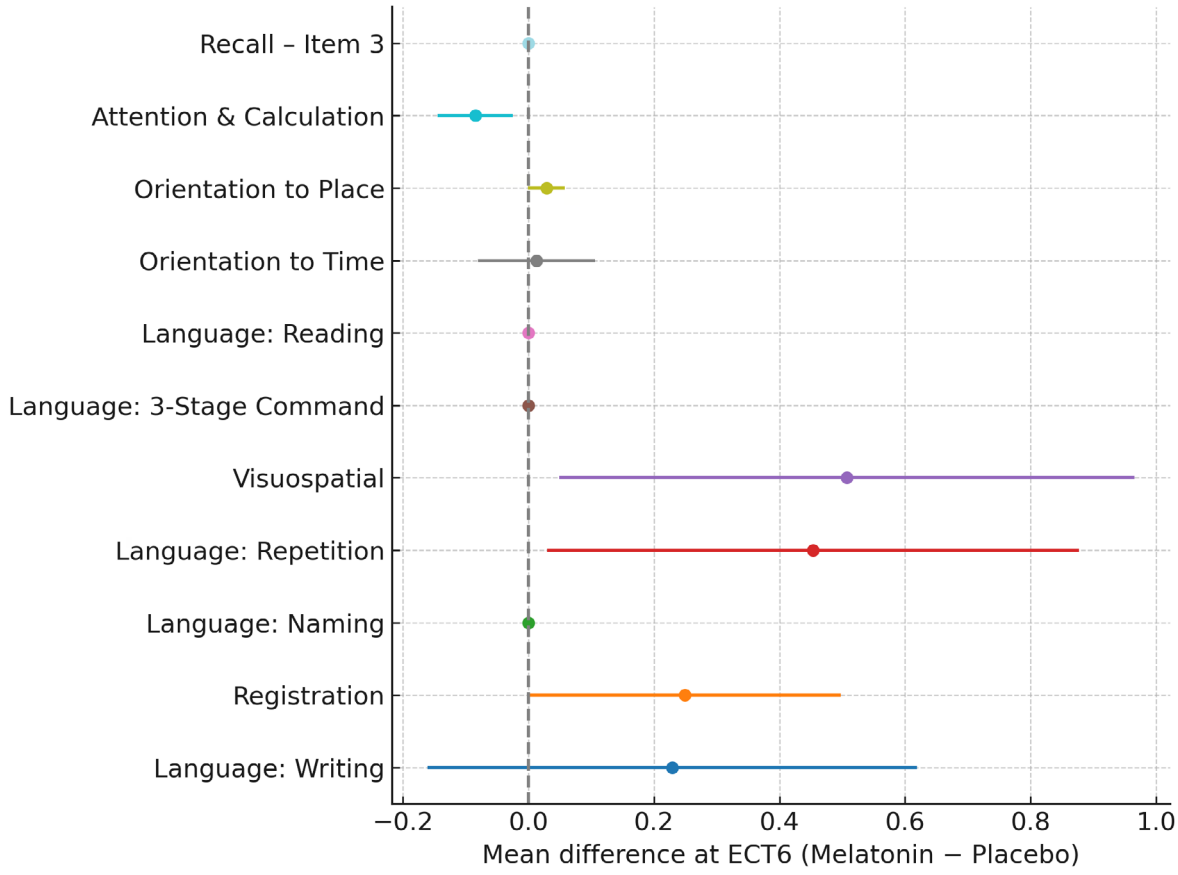

Figure 2. Subdomain-level MMSE outcomes

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A) Between-group differences at ECT6 (melatonin − placebo) with mean and 95% CI: Positive values favor melatonin; B) Difference-in-change (ΔMel − ΔPlac) from baseline to ECT6, showing net treatment effects: The largest benefits were seen in recall and attention & calculation, while language subdomains remained at ceiling.

events led to discontinuation of treatment or affected the ECT protocol. Overall, tolerability profiles were comparable between groups.

Discussion

Melatonin supplementation in our trial was associated with clear cognitive benefits and an excellent safety profile. In summary, patients receiving melatonin showed a significant improvement in overall cognitive performance (as measured by MMSE) compared to baseline and controls, with the most pronounced gains observed in the recall and attention & calculation subdomains of the MMSE. Notably, these cognitive improvements occurred without any detectable change in BP or other vital signs, and no serious adverse events were observed. This finding aligns with melatonin's known tolerability; it exerts minimal physiological side effects at therapeutic doses (Kołodziejska et al., 2025). The absence of hemodynamic effects or major side effects in our cohort underscores melatonin's safety and feasibility as a treatment option in this population.

Our findings can be contextualized alongside previous studies of both standard anti-dementia drugs and melatonin in related conditions. Cholinesterase inhibitors like donepezil are established treatments in Alzheimer disease (AD) and typically produce modest short-term cognitive improvements (on the order of ~1–2 points on the MMSE) in mild-to-moderate dementia (Sheikh & Ammar, 2024). For instance, a recent meta-analysis confirmed that donepezil 10 mg/d yields a significant MMSE increase (Hedges' g ≈2.3, 95% CI, 1.25%, 3.29%) versus placebo (Sheikh & Ammar, 2024), reflecting its symptomatic cognitive benefit. Memantine, an NMDA-receptor antagonist, is used mostly in moderate-to-severe AD and is known to have smaller effects on cognition but can help with behavioral symptoms like agitation and "sundowning" (Yaghmaei et al., 2024). Indeed, memantine's primary impact is often on neuropsychiatric and functional measures, whereas donepezil and other cho-

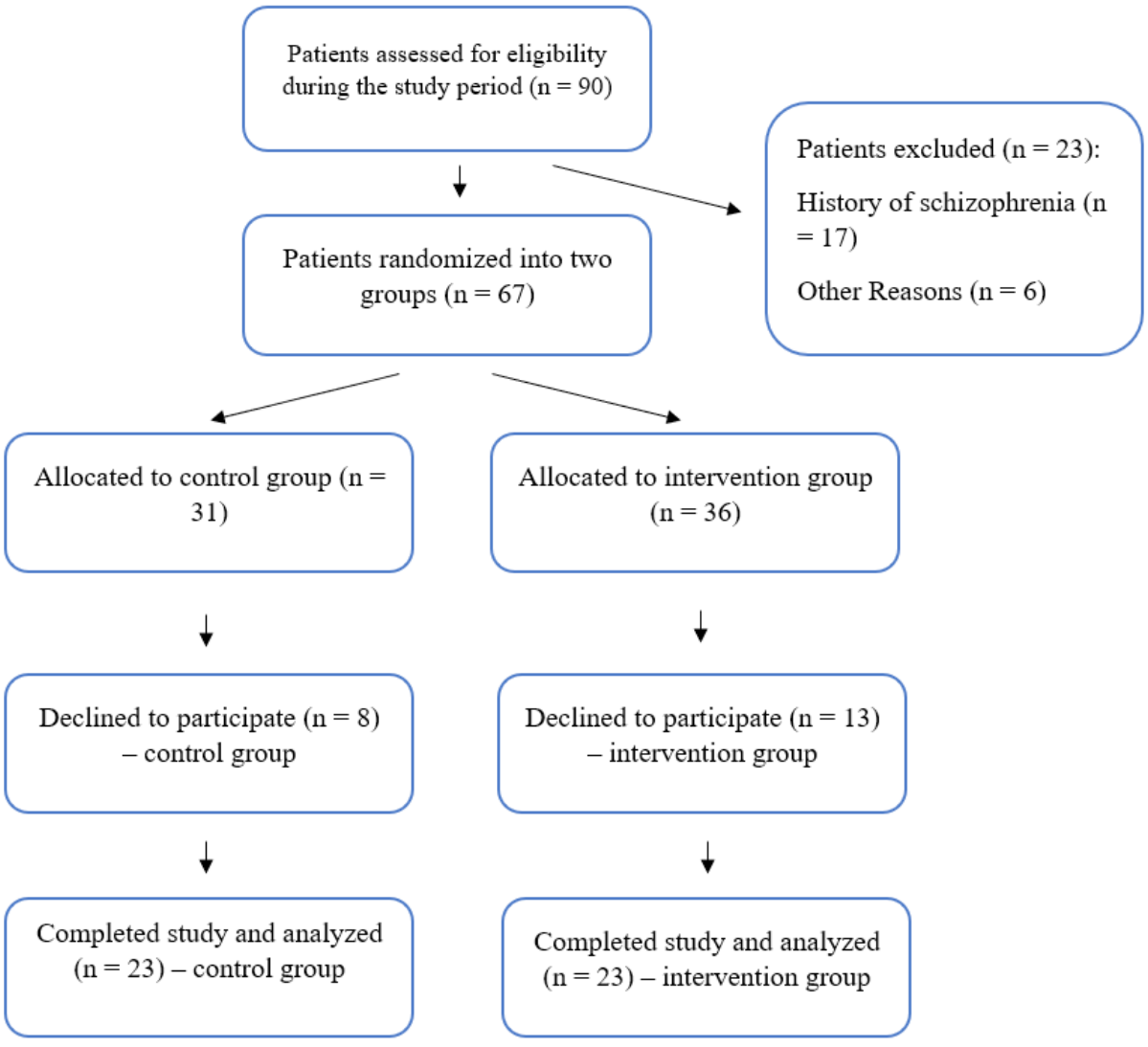

Figure 3. Blood pressure outcomes

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A) Line plots of mean SBP and DBP with 95% CIs at baseline and after the final ECT session (ECT6) in the melatonin and placebo groups, B) Bar plots of changes from baseline (ΔSBP, ΔDBP) with 95% CIs, illustrating net effects between groups

Note: No significant between-group differences were observed.

linesterase inhibitors directly enhance cognitive function by boosting cholinergic transmission (Yaghmaei et al., 2024). In comparison, the cognitive gains we observed with melatonin, particularly in memory recall and attention, are notable because they approach the magnitude of benefit seen with standard cognitive enhancers in mild dementia. A 2021 systematic review similarly found that >12 weeks of melatonin therapy in AD patients leads to a mean MMSE improvement of about 1.8 points relative to placebo (Sumsuzzman et al., 2021), especially in mild-stage AD. Such an effect size is comparable to that of cholinesterase inhibitors in early disease, suggesting melatonin's efficacy is not merely anecdotal. Historically, trials of melatonin for cognitive impairment have produced mixed results (Riemersma-van der Lek, 2008), with some early studies reporting no significant benefit. However, more recent evidence has shifted this perspective. For example, a network meta-analysis of dementia interventions concluded that melatonin may be a promising disease-modifying treatment for cognitive decline in mild AD and mild cognitive impairment (Modabbernia et al., 2011; Tseng et al., 2022; Wang et al., 2017; Xu et al., 2015). This finding implies that melatonin could offer more than symptomatic relief, potentially slowing neurodegenerative processes, a stark contrast to donepezil and memantine, which are primarily symptomatic treat-

ments. It is also worth noting that melatonin has been investigated in other clinical contexts of cognitive dysfunction. In post-ECT cognitive impairment (depressed patients undergoing electroconvulsive therapy), a head-to-head trial found melatonin (3 mg) was less effective than memantine (5 mg) at alleviating acute memory deficits (Sarraf et al., 2020). Melatonin recipients in that study actually showed a slight decline in MMSE post-ECT, whereas memantine-treated patients improved (Sarraf et al., 2020). This outcome highlights that melatonin's cognitive benefits may be context-dependent; it appears more useful in chronic neurodegenerative or age-related cognitive impairment than in preventing acute procedure-related deficits. Similarly, exploratory studies in surgical patients have hinted at neuroprotective effects of melatonin on postoperative cognitive dysfunction, particularly in memory and attention domains (Tavares et al., 2025). However, larger trials are needed for confirmation. Overall, our results strengthen the growing body of literature suggesting that melatonin can meaningfully improve cognitive function in conditions such as early AD or MCI (Sumsuzzman et al., 2021). A key distinction is that melatonin's benefits come without the cholinergic side effects (e.g. gastrointestinal upset) seen with donepezil or the neurologic side effects of memantine, making melatonin an appealing alternative or adjunct therapy. Given melatonin's different mechanism of action, there is also potential for combination therapy; just as donepezil plus memantine together yield better cognitive outcomes than either alone in advanced AD (Yaghmaei et al., 2024), melatonin might usefully complement standard drugs by addressing pathology (e.g. sleep disruption, oxidative stress) that those therapies do not.

Mechanistically, the cognitive enhancement observed with melatonin in our study is biologically plausible based on its neuroprotective actions. Melatonin is a pleiotropic molecule with robust antioxidant and anti-inflammatory properties in the central nervous system. It directly scavenges free radicals, inhibits lipid peroxidation, and stimulates antioxidant enzymes (such as superoxide dismutase and glutathione peroxidase), while concurrently suppressing pro-inflammatory signaling pathways (Kołodziejska et al., 2025). These actions help to protect neurons from oxidative stress and inflammation, factors strongly implicated in cognitive decline and dementia. Notably, melatonin has been shown to preserve synaptic function and prevent neuronal loss in hippocampal and cortical regions that subserve memory and attention. For example, preclinical studies demonstrate that melatonin can restore cholinergic neurotransmission in the hippocampus, increasing acetylcholine availability by upregulating choline acetyltransferase and other components of the cholinergic system (Chen et al., 2018). This finding corresponds well with our finding of improved memory recall (a hippocampal-dependent task) and enhanced attention/calculation, since the cholinergic system is crucial for both memory encoding and sustained attention. In AD models, melatonin has repeatedly shown the ability to reduce neuropathological burdens, attenuate β-amyloid accumulation and tau hyperphosphorylation, and limit microglial activation and the release of inflammatory cytokines (Kołodziejska et al., 2025; Zhang et al., 2025). Each effect could translate into preserved cognitive function. Reduced amyloid and tau pathology would help maintain synaptic integrity (hence better memory), and lower neuroinflammation could improve signaling in attention-related neural networks.

In addition, melatonin's role as a circadian regulator likely contributes to its cognitive benefits. Sleep and circadian rhythm disruptions are known to exacerbate cognitive impairment; poor sleep quality can hasten cognitive decline in older adults by aggravating β-amyloid deposition and other mechanisms (Tseng et al., 2022). Melatonin, by entraining sleep-wake cycles and improving sleep efficiency, addresses this often-overlooked aspect of brain health. Indeed, trials have found that melatonin (especially at low doses <5 mg) significantly improves sleep efficiency in patients with mild cognitive impairment and Parkinson's disease (Germain et al., 2023), and it is well recognized for improving insomnia in older adults. Better sleep, in turn, may sharpen daytime alertness and cognitive performance, particularly attention and executive function, which are highly sensitive to sleep loss.

Furthermore, during deep sleep, the brain's glymphatic system clears metabolic waste, including Aβ; melatonin's promotion of sleep could thus facilitate brain clearance of toxins that impair cognition (Zhang et al., 2025). Taken together, melatonin's antioxidant/anti-inflammatory effects and its normalization of circadian rhythms create a synergistic environment for cognitive improvement. The preferential gains we observed in memory and attention might reflect exactly these mechanisms at work – melatonin protecting the hippocampus and frontal cortex from oxidative injury while also ensuring the brain has restorative sleep to consolidate memory and support attention networks.

This study has several strengths that bolster confidence in the findings. To our knowledge, it is one of the first double-blind, placebo-controlled RCTs examining mela-

tonin's cognitive effects in this patient population. The double-blind design (blinding participants, caregivers/clinicians, and outcome assessors) minimizes bias in outcome reporting and assessment. Treatment adherence was high throughout the trial, and dropout rates were low, suggesting the intervention was acceptable to patients (likely owing to melatonin's benign side-effect profile). We also used a structured cognitive battery (MMSE with subdomain analysis) to detect domain-specific effects, which provided insight into where melatonin's impact is most pronounced (i.e. improvements in memory and attention). However, certain limitations must be acknowledged. The sample size was modest, and the trial was conducted at a single center, which may limit generalizability. A larger sample might have allowed detection of more subtle effects on other cognitive domains or subgroup differences. Our follow-up duration was relatively short (on the order of a few months); thus, we primarily captured short-term cognitive changes. It remains uncertain whether melatonin's benefits persist or deepen with longer-term use; longitudinal studies are needed to determine whether melatonin can slow the trajectory of cognitive decline over time.

Additionally, while we measured global cognition and simple subdomains, more sensitive neuropsychological tests (e.g. detailed memory tests or executive function tasks) were not included, which could have provided a finer-grained understanding of melatonin's cognitive effects. Finally, our exclusion criteria omitted patients with other major psychiatric comorbidities (such as schizophrenia or schizoaffective disorder), but the trial specifically enrolled patients with BD undergoing ECT. While melatonin is generally safe in BD, there remains some theoretical concern that exogenous melatonin could rarely precipitate manic episodes. However, no such cases occurred in our study.

Melatonin demonstrated a favorable safety profile and ease of use, emerging as a practical adjunct or alternative for cognitive impairment. It is inexpensive, widely available, and generally well tolerated, in contrast to prescription cognitive enhancers that often cause gastrointestinal or cardiac side effects. Our results suggest that a nightly regimen (5–10 mg) could benefit older patients with mild cognitive deficits, particularly when sleep disturbances or circadian irregularities are present. Improvements in memory and attention may translate into better daily functioning, and even stabilization of decline would be clinically significant.

Nevertheless, melatonin should be prescribed thoughtfully, with appropriate patient education on evening dosing and gradual onset of benefit. Caution is warranted in special populations, such as BD, where rare cases of mania induction have been reported (Bourin, 2024; McCarthy et al., 2022). Looking forward, large multi-center RCTs with longer follow-up are needed to validate these findings, define optimal dosing, and assess whether melatonin exerts disease-modifying effects.

Conclusion

This randomized, double-blind, placebo-controlled trial provides novel evidence that adjunctive melatonin can attenuate ECT-related cognitive impairment in patients with BD. Compared with placebo, melatonin was associated with significant improvements in global cognition, with the strongest effects in recall and attention/calculation domains, while maintaining an excellent safety profile. No major adverse events or hemodynamic changes were observed, underscoring its tolerability. These findings highlight melatonin as a simple, inexpensive, and widely accessible therapeutic option to support cognition in this vulnerable population.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Guilan University of Medical Sciences, Rasht, Iran (Code: IR.GUMS.REC.1402.080). The trial was prospectively registered by the Iranian Registry of Clinical Trials (IRCT), Tehran, Iran (Code: IRCT20220516054879N5). Written informed consent was obtained from all patients or their legal guardians before enrollment, following a detailed explanation of the study's objectives, procedures, potential benefits, and risks. All study procedures adhered to the ethical standards of the institutional review board and the principles of the Declaration of Helsinki.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. Due to ethical and privacy considerations, the data are not publicly available.

Declaration of generative AI and AI-assisted technologies in the writing process Funding

An AI-assisted tool (QuillBot) was used under the authors' supervision exclusively to improve academic language clarity and formatting. No AI tool influenced the scientific content, data analysis, or conclusions of this work.

Authors' contributions

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Conflict of interest

The authors declared no conflict of interest.

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Supplementary Table 1. Linear mixed-effects model results for total MMSE score across ECT sessions

Effect	Num df	Den df	F	P
Time	5	210	11.27	<0.001
Group	1	42	3.01	0.089
Group×Time	5	210	2.98	0.021

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MMSE: Mini-mental state examination; ECT: Electroconvulsive therapy.

Note: Model specification: Linear mixed-effects model with repeated factor "time" (6 levels: baseline to ECT6) and fixed factor "group" (melatonin vs placebo). Random intercepts per participant were included. The Kenward–Roger approximation was applied for denominator degrees of freedom.