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# Memantine in the prevention or alleviation of electroconvulsive therapy induces cognitive disorders: A placebo controlled trial

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ABSTRACT

The purpose of this study was to evaluate the effect of memantine administration on the adverse cognitive effects of electroconvulsive therapy (ECT). Forty patients diagnosed with a major depressive disorder for which ECT was indicated as a treatment for their current episode were randomly allocated to either the memantine (5 mg/day) group or the placebo group. All patients underwent the same protocol for anaesthesia and ECT procedures. The patients received memantine or the placebo for the whole period of ECT treatment, starting the day before ECT and continuing until the fourth session of ECT. The Modified Mental State Examination (MMSE) was used for the assessment of cognition before and after the trial. Regarding MMSE and item 3 MMSE (related to recent memory), the memantine group scored significantly higher at the end of ECT sessions than the control group ($P = 0.02$, $P < 0.001$, respectively). Our data support the hypothesis that memantine may reduce cognitive impairment following ECT. Memantine could be both a safe and well-tolerated treatment for use with ECT.



## 1. Introduction

Electroconvulsive therapy (ECT) is an effective method for the treatment of a variety of psychiatric disorders, especially depression (McCall et al., 2014). However, the cognitive abnormality induced by ECT is the major factor limiting its use in practice (Sackeim et al., 2007). ECT is associated with retrograde amnesia (reduced ability to recall recent events), anterograde amnesia (reduced ability for new learning) and prolonged postictal delirium and confusion (John et al., 2008).

The exact mechanisms contributing to ECT-induced cognitive deficits are not well determined. It has been shown that the cognitive deficits associated with ECT are directly related to the treatment and are not an adverse side effect of the anaesthesia that accompanies the treatment (Frith et al., 1983). It seems that ECT indiscriminately stimulates extensive parts of the brain and thereby induces changes in a wide range of molecular systems. Systems involved in learning and memory and for which ECT-related data are available include glutamatergic neurotransmission and *N*-methyl-D-aspartate (NMDA) receptor functioning, intracellular calcium, inflammatory processes and cholinergic transmission (Pigot et al., 2008).

The neuroprotective effects of a number of pharmacological agents have been studied in previous animal and clinical studies (Pigot et al., 2008). However, as yet, no pharmacological treatments have been proven to consistently attenuate ECT-induced memory impairment. Chamberlain and Tsai proposed a hypothesis involving glutamate and the NMDA receptor in ECT-induced memory impairment (Chamberlin and Tsai, 1998). Glutamate and NMDA receptors are involved in long-term potentiation (LTP), a fundamental process for memory consolidation, whereby brief high-frequency stimulation leads to an increased response after subsequent activation (Rita et al., 2008). This hypothesis explains the cascade of events that follow NMDA receptor depolarization. Magnesium antagonizes the NMDA receptor to calcium, and after removal of the blockade (during a seizure), calcium and water enter the cell, causing it to swell. This swelling temporarily impedes neurotransmission. There is also associated hyperactivity in reverberating pathways centring around the NMDA receptor and implicating cyclooxygenase 2, platelet activating factor, endogenous

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cannabinoids and prostaglandins; this hyperactivity results in a reversible oxidative stress. The net result of all these mechanisms is a transient cognition dysfunction (Andrade et al., 2008).

The well-documented ability of NMDA antagonists to slow the cognitive dysfunction in patients with Alzheimer's disease (AD) (Corbett et al., 2010) suggests that they may have the potential to alleviate or prevent cognitive abnormality secondary to ECT. Also combination of cholinergic agents with memantine would be better than either alone in alleviation of cognition disorders. For example Atri et al. have shown that combination treatment with memantine added to donepezil in patients with moderate to severe Alzheimer's disease is associated with significant benefits in reducing 24 weeks decline in cognition, function and global status (Atri et al., 2013). In another study, the combination of galantamine and memantine was effective in schizophrenia in order to increase the selective cognition enhancement produced by either medication alone (Koola et al., 2014).

Ketamine is an NMDA antagonist that has attracted attention for the induction of anaesthesia during ECT in recent years. Yoosefi et al. evaluated the effect of ketamine and thiopental in patients undergoing ECT. They used Mini-Mental State Examination (MMSE) scores for the evaluation of memory dysfunction. They reported that despite a significant decline in MMSE scores in both groups after the first ECT, cognitive function improved afterwards, but the difference was significant only in the ketamine group (Yoosefi et al., 2014).

Memantine is a non-competitive NMDA receptor antagonist that is approved by the United States Food and Drug Administration for the treatment of moderate to severe Alzheimer's disease. It has shown modest benefits in cognition, function, global and behavioural measures and has shown a low potential for drug interactions (Herrmann et al., 2011). The aim of this pilot study was to evaluate the potential use of memantine in the alleviation or prevention of cognition impairment in patients undergoing ECT. We were also interested in exploring the safety and tolerability of memantine in patients receiving ECT.

## 2. Materials and methods

### 2.1. Study design

The study was a prospective, double blind placebo controlled trial included 40 patients. Ethical committee approval was obtained from the Shahid Beheshti University of Medical Sciences before starting the study as per the provision of the Helsinki declaration (2000). Also the trial was also registered in the Australia and New Zealand Clinical Trial Registry (ANZCTR) with number ACTRN12614000619640.

The study setting was the psychiatry department of Taleghani Hospital, affiliated with Shahid Beheshti University of Medical Sciences, Tehran, Iran. This is a well-known center for the treatment of psychiatric patients in Iran. The criteria for inclusion in the study were a comprehensive psychiatric evaluation in which the patient met the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for major depressive disorder for which electroconvulsive therapy (ECT) was indicated as a treatment for their current episode. The severity of participant's depression was also determined using the Hamilton Depression Rating Scale (HAM-D). Patients included in the study had a baseline HAM-D of at least 20. The HAM-D is the most widely used physician-administered rating scale for depression. The scale summarizes 17 individual scores to provide a total score that indicates the severity of depression (Hamilton, 1960). All study participants signed consent forms after the study procedures were explained. Criteria for exclusion from the study were history of schizophrenia, schizoaffective disorder, or bipolar disorder I or II, or rapid cycling bipolar disorder. Patients with heart conduction dysfunction, bradyarrhythmia, renal or hepatic impairment, seizure disorders, or opioid dependency were also excluded from the study. Furthermore, patients who received cholinergic agents, COX-2 inhibitors, calcium channel blockers, nootropic agents or glucocorticoids before or during the study were also excluded.

### 2.2. ECT protocols

ECT was performed using a square-wave, brief pulse, constant current device (MECTA 5000). The patients received memantine or the placebo for the whole period of ECT treatment, starting the day before ECT and continuing until the fourth session of ECT. As ECT was done every other day in all participants, the duration between the first ECT and the fourth ECT was 8 days. Anaesthetic agents included propofol (AstraZeneca, England) at an average dose of 0.5–1 mg/kg, succinylcholine (Caspain, Iran) 20 mg and atropine (Alborzdaru, Iran) 0.5 mg. The placement of electrodes was right unilateral, following the standard D'Eliaplacement. For all subsequent treatments, stimulus intensity was maintained at 50–100% above the initial seizure threshold. A custom-modified MECTASR-1 was used for stimulus delivery. Vital signs were examined prior to and during the 5 min period following seizure termination. The stimulus frequency was 90 Hz and the stimulus duration ranged from 1 to 4 s. Seizure monitoring was done using a two lead electroencephalogram of the right and left hemispheres as well as visual monitoring of residual motor convulsive activity.

### 2.3. Measures

Forty study participants (23 female, 17 male; mean (±SD) age, $39.07 \pm 11.87$ years) undergoing ECT completed the study. The participants, who were admitted to receive ECT, were given 5 mg/day of memantine or a placebo beginning the day before the first session of ECT until the fourth session of ECT. A sequence was computer-generated to randomly assign patients to two groups in a 1:1 ratio. This sequence was generated in blocks of 4, 8 and 12 using the 'blockrand' extension of the R Project software package. Knowledge of this sequence was available only to a nurse not involved in volunteer recruitment. This nurse allocated patients to either the placebo group or the memantine group by flipping a coin. Next opaque boxes were filled with either placebo or memantine tablets and sealed and numbered to correspond to the computer-generated sequence. While patients underwent volunteer recruitment by the medical staff, each was assigned a number that corresponded sequentially to a treatment box. Therefore, a strategy of numbered boxes was used for sequence concealment. A test to measure cognitive functioning, the Modified Mental State Examination (MMSE), was administered to patients both pre-ECT and post-ECT. Pre-ECT ratings were measured 24 h before the first ECT treatment, and post-ECT ratings were measured 24 h after the last ECT treatment.

MMSE can be used to reliably detect and monitor memory dysfunction during ECT sessions and in the weeks following the cessation of treatment. Pre-ECT MMSE scores may be useful to predict the severity of memory dysfunction during and shortly after ECT (Nehra et al., 2007). The MMSE consists of 12 items, and has a highest score of 30, with the score inversely related to cognitive abnormality. A score higher than 24 usually indicates no cognitive impairment, and scores lower than 23 usually indicate some degree of cognitive impairment. MMSE is a simplified scored form of the cognitive mental status examination and requires only 5–10 min to administer. Thus the MMSE is practical for routine, repeated use (Folstein et al., 1975). Item 3 in the MMSE questionnaire on recent memory was used to assess the 2 groups. In item 3 of the MMSE, the examiner names three unrelated objects clearly and slowly, then asks the patient to repeat all three. The

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